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VOLUME 81 NUMBER 6

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JUNE 1948

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879. Additional entry at Nashville, Tenn.

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Archives of Internal Medicine

VOLUME 81 JUNE 1948 NUMBER 6

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PHEOCHROMOCYTOMA WITH SYMPTOMS OF EPINEPHRINE SHOCK

Report of a Case

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AND
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PHILADELPHIA

The clinical syndrome associated with pheochromocytoma of the adrenal gland is well recognized and the modern literature contains records of cases in which the condition was diagnosed and surgically treated and the patient cured. However, the classic symptoms are not invariably present, and occasionally this tumor is accidentally discovered at autopsy apparently unassociated with any symptom pattern or with the cause of death. In some instances medical aid is not sought until the terminal fulminating episode, during which the patient may present a variety of symptoms which tax the ingenuity of the most astute diagnostician. Such was the nature of the case to be presented.

REPORT OF A CASE

A 32 year old soldier, assigned to duty in India, became suddenly ill on Aug. 29, 1945, at 9 a.m., with palpitation, dyspnea, epigastric pain, nausea and vomiting. The vomitus was watery in consistency, and, according to the patient, blood tinged. The soldier remained in his quarters, where he was first examined by a medical officer. At that time the only essential finding was a tachycardia of 120, with a regular pulse rate of fair volume. He did not appear acutely ill and so was permitted to remain in quarters. However, several hours later his condition became worse. He appeared pale and was drenched with perspiration. The epigastric pain persisted but was somewhat alleviated by changing positions. The temperature was 100.2 F., the pulse rate 120, the respirations 44 and the blood pressure 140 systolic and 120 diastolic. Widely dilated pupils were observed which reacted sluggishly to light. There were moist rales throughout the lower lobes of both lungs. The heart rate was rapid and regular, but no abnormal sounds were elicited. A mottled cyanosis of the extremities was conspicuous. Abdominal examination revealed nothing significant.

From the Twentieth General Hospital, India.
Dr. Ferraro is a pathologist at St. Francis Hospital, Poughkeepsie, N. Y.

On his admission to the hospital, 0.032 Gm. of morphine sulfate was administered hypodermically and external heat applied to the body. Oxygen therapy was instituted continuously. He appeared to improve slightly under this regimen, but this change was temporary. By 7 p.m. that day the temperature reached 104.2 F. and the pulse rate, barely perceptible, 156. In view of this unexplained temperature, 50,000 units of penicillin was administered. However, alarming symptoms soon appeared. The cutaneous surfaces became cold, especially over the extremities, and profuse perspiration continued. Later, shallow respirations, progressive cyanosis, a temperature of 106.4 F. and coma developed. Death occurred at 11:40 p.m., fourteen hours after the onset of his symptoms.

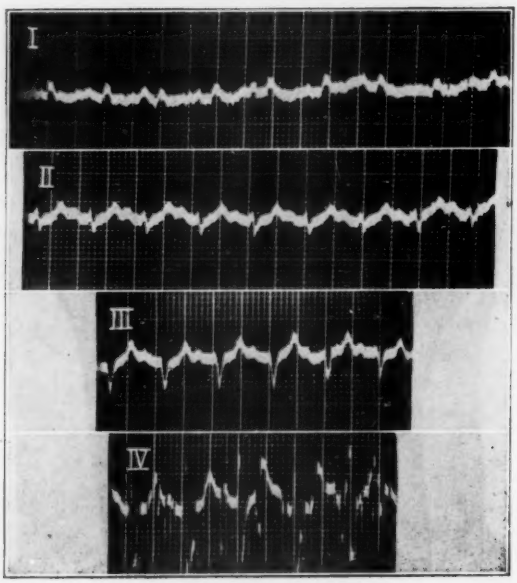

Fig. 1.—Electrocardiogram showing left axis deviation and sinus tachycardia. (Seventh Medical Museum and Arts Department negative no. G-4592.)

The laboratory data were as follows: The red blood cell count was 6,300,000 and the white blood cell count 20,000, with 82 per cent polymorphonuclear cells, 8 per cent lymphocytes and 10 per cent monocytes. The electrocardiograph (fig. 1) showed a rate of 122 and a QRS wave of 0.08 seconds.

The QRS wave in lead I was splintered, in lead II diphasic and in lead III inverted; the T wave was upright. This was interpreted as indicating (1) left axis deviation and (2) sinus tachycardia.

Subsequent to the death of the patient, additional significant history was obtained from a friend, who informed us that the patient had experienced several attacks of palpitation while on board ship en route to India. These attacks lasted several hours and subsided spontaneously. There is no available information regarding either the physical findings or the therapy instituted on these occasions.

Observations at Necropsy.—The essential findings at necropsy are summarized as follows:

Heart: The heart weighed 400 Gm. The first inch of the left anterior descending artery revealed a prominent eccentric atheromatous deposit producing a crescentic narrowing of the lumen.

Left Adrenal Gland: A large encapsulated tumor conspicuously occupied the position of the left adrenal gland and measured 7 by 5 by 4 cm. It weighed 70 Gm. At the superolateral border a compressed and displaced portion of the adrenal gland was noted merging imperceptibly with the mass. The latter was reddish brown,

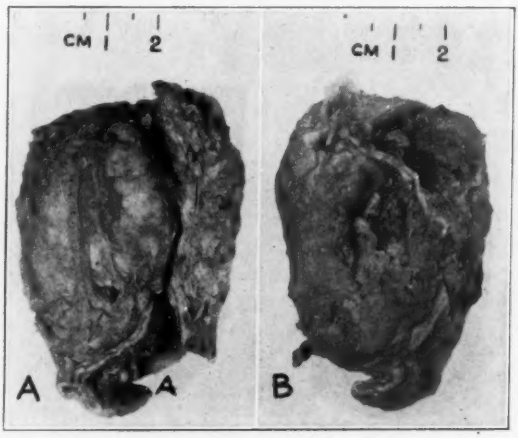

Fig. 2.—*A*, surface view of the tumor. Compressed portion of adrenal at *A*. *B*, cut section of tumor revealing pseudocystic cavities. (Seventh Medical Museum and Arts Department negative nos. A-451081-1 and A-451081-2.)

tensely cystic and completely encapsulated. On section, about 10 cc. of dark hemorrhagic fluid was released under pressure. Two irregular pseudocystic cavities occupied the central region, surrounded by a rim of soft golden yellow and brownish tissue.

Right Adrenal Gland: This was normal on gross examination.

Other Organs: The rest of the organs did not show any significant changes.

Microscopic Examination: Section of the tumor revealed a diffuse proliferation of normal-appearing chromaffin cells surrounded by a delicate fibrous stroma in which occasional dilated capillaries were noted. The diagnosis was pheochromocytoma.

COMMENT

The pathogenesis of "epinephrine shock" in pheochromocytoma is not understood in its entirety although several important experimental, clinical and pathologic observations have helped to clarify this condition.

Freeman, Freedman and Miller[1] succeeded in producing shock by the continuous injection of epinephrine in unanesthetized dogs. They described symptoms of moderate hyperpnea and restlessness shortly after injection, with vomiting as a frequent occurrence. At the end of one

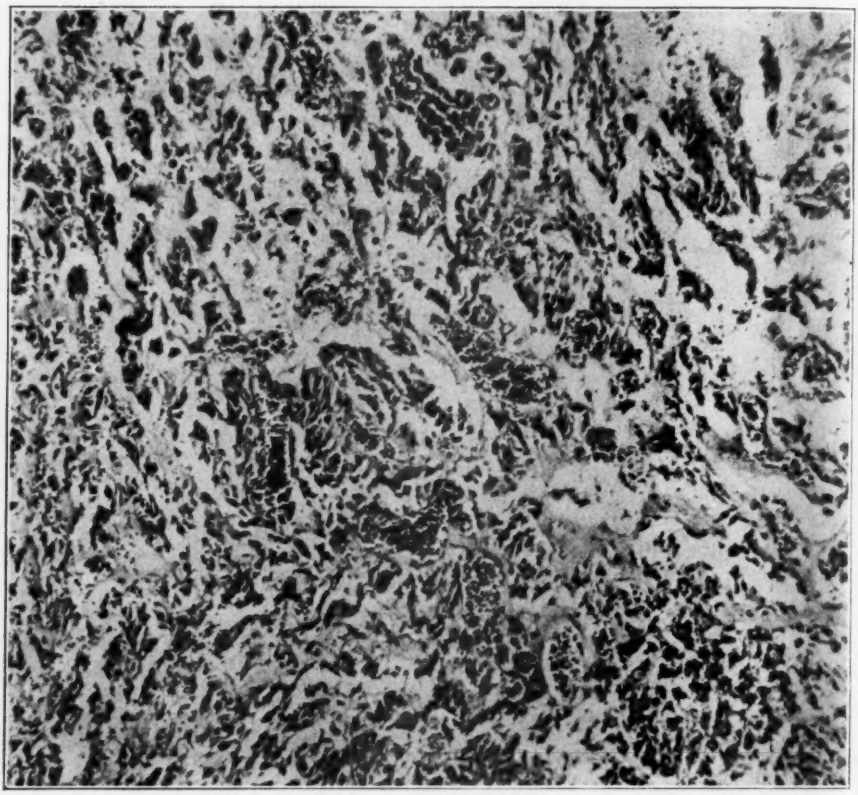

Fig. 3.—Masses of chromaffin cells surrounded by an irregular fibrous stroma; low power magnification. (U. S. Army Medical Museum negative no. 90714.)

hour, clinical symptoms of shock were marked. Other symptoms noted were pallor, cyanosis, coldness of the ears and extremities, thready pulse, rapidly rising temperature, excessive hypertension later subsiding and decreasing plasma volume. The latter was thought to be initiated by anoxia of the peripheral capillaries following prolonged vasoconstriction, eventuating in a loss of fluid into the tissues. These authors emphasized the altered status of the plasma proteins as a mechanism in the

1. Freeman, N. E.; Freedman, H., and Miller, C. C.: Production of Shock by Prolonged Continuous Injection of Adrenalin in Unanesthetized Dogs, Am. J. Physiol. **131**:545-553 (Jan.) 1941.

production of shock and were able to relieve this condition in several dogs by the use of blood transfusions and the intravenous injection of hypertonic solution of dextrose.

From the clinical standpoint, it is generally agreed that "epinephrine crises" are associated with a characteristic group of symptoms among which may be mentioned hypertension, coldness of the extremities, with blanching or mottling of the skin, diaphoresis, accelerated

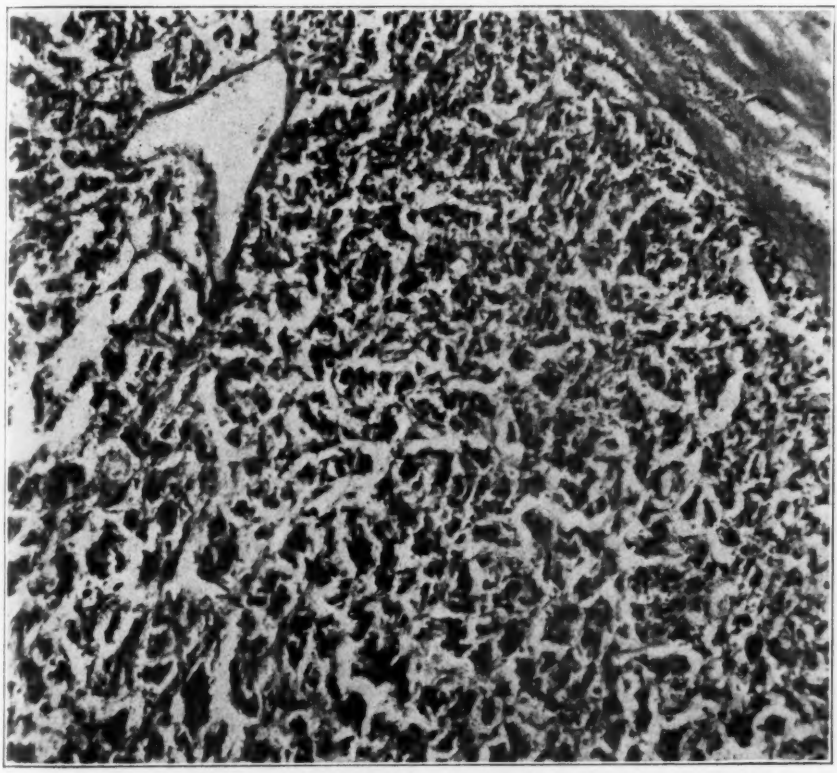

Fig. 4.—Typical pattern of chromaffin cells; high power magnification. (U. S. Army Medical Museum negative no. 90713.)

heart rate, dyspnea and varying degrees of shock. These symptoms have been found in a sufficiently large number of proved cases to warrant the assumption of a direct relationship with the pheochromocytoma.

The demonstration of a pressor substance during a crisis has not met with universal success. This is readily understood when the relatively small amount of the offending substance, presumably epinephrine, in the circulating blood is appreciated, as well as the difficulty of its

identification. However, in 1937, Beer, King and Prinzmetal[2] reported a case of pheochromocytoma and demonstrated the presence of a pressor substance in the blood. After the surgical removal of this tumor, no similar substance could be recovered from the plasma.

Pathologic studies of surgical specimens and of speminens at autopsy have established certain fundamental facts. First, the tumor is composed of hyperplastic chromaffin cells duplicating the appearance of the normal adrenal medulla. A few malignant tumors have been recorded, but these are rare. Secondly, chemical tests applied to the tumors at the time of removal have indicated the presence of epinephrine in increased amounts. Kalk[3] reported the findings of 375 to 500 mg. of epinephrine in a neoplasm of this type as compared to a normal of approximately 4 mg. Belt and Powell[4] reported a case in which the tumor yielded 2 Gm. of epinephrine per hundred grams of tissue.

Thus it appears that the syndrome during an "epinephrine crisis" results from an abnormal release of epinephrine into the general circulation. The initiating factors capable of inducing this state may vary, although mechanical pressure over the site of the tumor and physiologic stimuli such as fear, anger or excitement are frequent offenders. In view of the paroxysmal nature of these attacks, it must be assumed that during the interim state of well-being, the release mechanism is held in abeyance.

SUMMARY

1. A case of pheochromocytoma which terminated fatally after "epinephrine shock" is reported.

2. Experimental, clinical and pathologic evidence is submitted for the explanation of this syndrome.

Gen. Isadore Ravdin and Col. Francis Wood granted us permission to report this case.

2. Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, Ann. Surg. **106**:85-91 (July) 1937.

3. Kalk, H.: Paroxysmale Hypertension: Blutdruckkrisen und Tumor des Nebennierennorkes, Klin. Wchnschr. **13**:613-617 (April 28) 1934.

4. Belt, A. E., and Powell, T. O.: Clinical Manifestations of Chromaffin Cell Tumors Arising from Suprarenal Medulla: Suprarenal Sympathetic Syndrome, Surg., Gynec. & Obst. **59**:9-24 (July) 1934.

TROPICAL ANHIDROTIC ASTHENIA

Its Definition and Relationship to Other Heat Disorders

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If it be a turbulent, rough, cloudy, stormy weather, men are sad, lumpish, and much dejected, angry, waspish, dull and melancholy.—*Robert Burton.*[1]

Why does long residence tend to annul adjustment to the tropics? The explanation is complex and involves many functions of both mind and body.[2] Inasmuch as all authorities agree that man needs efficient sweat glands, it is odd that disorders of sweating have failed to gain full notice in relation to the vicious results of heat. Despite intense study of the normal activity of the sweat glands, it has hitherto been true that little was known of the ill effects of their incompetence on tropical health. Such information as was available dealt chiefly with congenital deficiences of the glands. But the congenital disease is a medical curiosity, and its study solves little of the larger problem of acquired intolerance to heat.

However, as a result of the recent war several reports have appeared which describe a temporary failure of sweating (anhidrosis)[3] and the general disability which results therefrom. It would seem that there exists a newly recognized syndrome of heat exhaustion associated with and probably caused by an anhidrosis of a large part of the body's surface. The disease, which constitutes a specific form of tropical deterioration, is more subtle than the classic heat disorders and easily eludes detection.

It has been reported from several parts of the world by three different teams. Wolkin, Goodman and Kelley,[4] working in the Amer-

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1. Shilleto, A. R.: The Anatomy of Melancholy, London, George Bell and Sons, 1893, pt. 1, sect. 2, memb. 2, subsect. 5.

2. Kark, R. M., and others: Tropical Deterioration and Nutrition: Clinical and Biochemical Observations on Troops, Medicine **26**:1 (Feb.) 1947.

3. This word, meaning decrease or failure of sweating, is also spelt "anidrosis" or "anhydrosis." Although somewhat cumbersome, "anhidrosis" appears to have the widest usage.

4. Wolkin, J.; Goodman, J. I., and Kelley, W. E.: Failure of the Sweat Mechanism in the Desert: Thermogenic Anhidrosis, J.A.M.A. **124**:478 (Feb. 19) 1944.

ican desert area, called it "thermogenic anhidrosis." Ladell, Waterlow and Hudson[5] reported it from Southern Iraq under the name "heat exhaustion, type II." Allen and O'Brien[6] observed it in the South West Pacific area and gave it the name "tropical anhidrotic asthenia." Recently,[7] I have given a further account of anhidrotic asthenia, chiefly from the points of view of etiology, histology and treatment. The present paper, which is based on the one just mentioned, includes some more clinical features and, in particular, integrates my own observations with those of others. Critical correlation may be useful as there is often difficulty in deciding which elements truly belong to a newly described entity and which do not.

Stuart D. Allen[6] was the first to recognize the syndrome in soldiers who were stationed in the Northern Territory of Australia. Six patients admitted to hospital under his care early in 1943 gave a similar history of exhaustion, headache and dyspnea when working in the heat. Most had suffered from miliaria rubra (prickly heat) a short time before the onset of general symptoms. Allen noted the dry skin and the goose-flesh-like rash which these subjects characteristically show on exertion.

The present account is based on 38 typical severe cases observed over three wet seasons and includes, by permission, those which Allen originally found and demonstrated. This total is only a small, undetermined fraction of the cases which actually occurred amongst Australian troops in the South West Pacific. Indeed, because of service memorandum,[8] most Australian medical officers in the area were able to recognize the disease, if only in a mild form, among troops under their own care. Besides those in the Northern Territory of Australia, I have seen patients at Merauke (Dutch New Guinea)[9] and Morotai (Moluccas) and others evacuated from Dutch Borneo. Novy and Ramsey[10] encountered 2 cases in New Guinea and Ginsberg,[11] 3 at Cape

5. Ladell, W. S. S.; Waterlow, J. C., and Hudson, M. F.: Desert Climate: Physiological and Clinical Observations, Lancet **2**:491 (Oct. 14); 527 (Oct. 21) 1944.

6. Allen, S. D., and O'Brien, J. P.: (*a*) Tropical Anhidrotic Asthenia, M. J. Australia **2**:335 (Sept. 23) 1944; (*b*) abstracted, Bull. War Med. **5**:486 (April) 1945.

7. O'Brien, J. P.: A Study of Miliaria Rubra, Tropical Anidrosis and Anhidrotic Asthenia, Brit. J. Dermat. **59**:125 (April-May) 1947.

8. O'Brien, J. P.: Dysfunction of the Skin in the Tropics, a memorandum prepared in 1944 for the Director-General and distributed officially within the Australian Army Medical Corps.

9. The average weather conditions in the wet season at Merauke, where most of the present work was done, were as follows: The maximum temperature (afternoon) was 90 F. and the relative humidity 65 per cent. The minimum temperature (early morning) was 65 F. and the relative humidity 100 per cent.

10. Novy, F. G., Jr., and Ramsey, J. H.: Failure of the Sweat Mechanism in the Desert, J.A.M.A. **125**:738 (July 8) 1944.

11. Ginsberg, M. W.: Personal communication to the author.

York (Australia). More recently, Sulzberger, Zimmerman and Emerson[12] have found and investigated the disease in the United States Navy on Guam. It is more prevalent than superficial observation would suggest. By means of regular inspections, Kendall[13] detected 28 cases among 440 members of a battalion in Merauke during ten months of 1944—an incidence of 6 per cent. All the affected men were not sick enough to need treatment in hospital, but at best they were unable to continue full duty. There seems little doubt that the disease can occur wherever severe miliaria is found. Mild cases and cases in which the subjects show only the cutaneous signs (simple tropical anhidrosis)[7] are frequently observed.

The onset of the disease is rather insidious, although it may be acute in those who have had a particularly intense, diffuse attack of miliaria. When the speed of onset is being estimated, it should be kept in mind that the disease can be present but not manifest until such time as the subject undertakes physical exertion. Typically, the patient notices, over a period of a week or two, that exercise in the heat of the day, especially in bright sunshine, produces an unusual degree of exhaustion and sensation of heat as well as throbbing frontal headache, giddiness, dyspnea and palpitation; if the exertion is continued, transient dimness of vision may occur. In other words, the subject shows an excessive fatigue response to exercise. Fainting is not a feature unless the earlier warning symptoms have been unheeded. True coma does not occur. When the disease is severe, exercise, such as wood chopping, is impossible for more than a few minutes.

Subjectively, the skin is hot as though burning and has a feeling of fulness or tenseness. Pruritus may be present but only, as a rule, when some miliarial lesions still persist from the antecedent attack. In practically every instance the patient states that the pruritus of miliaria has improved by the time general symptoms begin, and in some cases no sensations of the skin are felt during the phase of general symptoms.

The patient sometimes notices that the trunk and limbs are dry. More often he comments on the profuse sweating (hyperhidrosis) which regularly appears from the forehead and face during exercise. Sweat runs into the eyes from the forehead and onto the chest from the neck and chin. This heavy sweating from the exposed parts of the head often deludes both subject and observer into believing that sweating generally is not diminished.

On examination, the patients are exhausted, frequently to the extent that tremor, and incipient fainting are observed. The respirations are

12. Sulzberger, M. B.; Zimmerman, H. M., and Emerson, K.: Tropical Anidrotic Asthenia (Thermogenic Anhidrosis) and Its Relationship to Prickly Heat, J. Invest. Dermat. 7:153 (Aug.) 1946.

13. Kendall, B.: Personal communication to the author.

increased in depth, and the rate is up to 50 excursions per minute, the pulse is accelerated to an average of 160 beats per minute and the oral temperature is raised to an average of 100 F. (37.8 C.). The highest oral temperature recorded in the present series was 102.6 F. (38.9 C).

The cutaneous changes are characteristic, providing they are looked for immediately after exercise; they are less striking at other times. Most or all of the covered parts are partly or completely devoid of sweat and studded with innumerable deep, matt white vesicles,[14] each 1 mm. or less across, the general effect being like that of goose flesh. However, the vesicles do not surround hairs as do the elevations of true goose flesh. The intervening skin is not red. Superficial miliarial vesicles with red areoli and red miliarial papules may still be present, either in isolated groups or else scattered thinly among the more numerous typical lesions. To touch, the skin is hot, thickened and particularly dry.

The palms and soles are never affected by the rash and in most instances sweat normally but not profusely. The axillas and the folds of the groin may or may not be dry. On the legs, ichthyoid changes are more common than a typical rash. A fairly constant feature is a moderate, persistent enlargement of the axillary and inguinal lymph glands. The relative or complete dryness of the covered parts and the associated rash are regarded as pathognomonic when taken in conjunction with the asthenic symptoms and signs.

When the patient lies in a cool place the various manifestations pass off in from half an hour to three hours. If it is extremely hot, the rash may persist but in a less obvious form. Should further exercise be undertaken, the clinical picture soon reappears exactly as before.

Apart from the discomforts of physical exercise, the patient may feel fairly comfortable and be able to carry out light duties. However, some continuous lack of appetite and in the day's heat some listlessness and headache are often felt. Frequency of micturition and polyuria are occasionally noticed, though more usually urinary symptoms have largely passed off by the time the patient reports ill.

The duration of the disease when untreated is variable, but as a rule it is at least four and sometimes twelve weeks before normal sweating is restored and the patient can undertake exertion without discomfort. In some instances the disease progresses and the subject is exhausted by the slightest effort. One attack does not confer immunity.

The pathogenesis of the goose-flesh-like rash has been described independently by Sulzberger and others[12] and by O'Brien.[7] Here it need only be pointed out that each vesicle is caused by the localized escape of sweat into the dermis from a blocked, ruptured sweat duct. The

14. Clinically the lesions simulate papules. Histologically[7] they are vesicles and are due to localized extravasations of sweat into the dermis.

clinical and histologic evidence has shown conclusively that the rash and the associated anhidrosis are the end results of previous miliaria. Indeed, the rash represents the chronic phase of occlusion of the sweat glands, the acute phase being miliaria rubra itself. New descriptive terms seem to be required for the lesions other than the well known vesicles and papules of miliaria. Henceforth the lesions which resemble goose flesh are called anhidrotic vesicles. The rash is called the anhidrotic rash,[15] whereas the associated anhidrosis is called tropical anhidrosis. The term anhidrotic asthenia is used only when the tropical anhidrosis is severe enough to cause general symptoms.

A detailed analysis of the symptoms and signs noted in the present series of cases is given in panel D of table 1. The subjects had been in the tropics for an average of six and a half months before they commenced to suffer from miliaria. The average interval between the commencement of miliaria and the first general symptom of anhidrotic asthenia (usually exhaustion) was eight weeks. In some cases there was no interval, that is, according to the patient both the miliaria and the general symptoms commenced together, and in others it ranged up to twenty-four weeks. This large range of variation is probably caused by a number of factors which may themselves vary and which include the current weather and the activity and the psychologic nature of the subject. However, the most important factor would appear to be the number of sweat glands implicated by the antecedent attack of miliaria. In regard to this point, most persons suffer from miliaria in only a moderately severe form, and it occurs in progressive or recurring waves which chronically obstruct groups of sweat glands in turn. When this is the case, the latent period between the onset of miliaria and the general symptoms tends to be long and indefinite. In a smaller number of cases a single attack of miliaria involves most of the sweat glands; in such instances, the latent interval is short. The interval which usually elapses between the cessation or improvement of the miliaria and the onset of the general symptoms of anhidrotic asthenia is not recorded as it varied much and was often difficult to assess from the patients' impressions. The same applies to the patients' statements on the duration of the

15. Histologically, the vesicles and rash are perhaps more correctly described as dyshidrotic and not anhidrotic in nature. However, the word "dyshidrosis" has been used in the past for other conditions and is therefore best avoided. Moreover, the anhidrosis associated with the rash is its most significant feature, and it therefore seems necessary to suggest this relationship. A term "miliaria alba" is sometimes found in the literature (Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 9, St. Louis, C. V. Mosby Company, 1935, p. 1185) but seems to have largely passed out of use. As no complete description is available, its affinity to the anhidrotic rash is doubtful. Nevertheless, miliaria alba and the anhidrotic rash are probably identical. Because it lacks functional significance, reintroduction of the obsolete "miliaria alba" is not recommended.

TABLE 1.—*Symptoms and Signs on Exposure to Heat and Exertion (Comparative Data from All Authors)*

Author and Place	No. of Cases	Exhaustion	Sensation of Excessive Heat	Headache	Vertigo	Dyspnea	Palpitation	Dimness of Vision ("Blackout") and Syncope	Gastrointestinal Symptoms
A. Wolkin and others "Thermogenic Anhidrosis" (North American Desert)	8	+	+	+	+	Not mentioned	No mention	Two had short attacks of syncope	Nausea in a doubtful case (case 6)
B. Ladell and others "Heat exhaustion, Type 11." (Desert of Southern Iraq)	55	+	Not mentioned (can be presumed to have been present—skin hot clinically)	No mention	+	Present in 23 of 55 cases	Palpitation and precordial pain in 2 cases	Dimness of vision not mentioned; apparently no syncope	Vomiting and cramps in 4%, anorexia
C. Sulzberger and others (Guam)	1	+	+	+	+	+	No mention	+	No mention
D. Present Series* (South West Pacific)	38							Dimness of vision on exertion present in about 50% of patients, usually shortly before they reported ill; occasionally complete syncope	In some cases anorexia or nausea; epigastric discomfort present in 2 cases; no vomiting or cramps
1. Average duration of symptoms before reporting ill (days)		19	Duration not recorded	21	20	14	19		
2. Range of variation (days)		2–90		1 to 90	2 to 90	1 to 30	2 to 90		
3. Percentage of cases affected		100	100	80	80	70	70		

*The data here are calculated only from those cases in which the presence or absence of the symptom was recorded in the notes.

	Anhidrosis on Clothed Areas	Anhidrotic Rash (Goose-Flesh-Like Rash)	Profuse Sweating on Forhead and Face	Frequency and Polyuria	Miliaria	Desquamation	Pilocarpine Test	Enlarged Lymph Glands	Miscellaneous
A.	+	+	+	No mention	Definite history in 1 case; no note in remainder	In long-standing cases	No response on dry areas	No mention	Onset of disease seemed sudden; condition improved as rash disappeared
B.	History of "defective sweating" in 87%; "dry skin "on examination in 40%	No specific mention; "lichenification"; prickly heat in "healing or desquamating" stage	+	Definite and extremely common	80% had rash on admission to the hospital, moderately severe or severe	Severe	Apparently not used	No mention	Tachycardia; insomnia; duration in hospital, 10 to 20 days
C.	+	+	+	Indefinite	Extremely severe	Not mentioned	Not mentioned	Tender; enlarged?	
D.	Partial or complete in 100% of cases	Present in 100% of cases on dry parts	All cases	Present but not conspicuous	History in all except 2 cases, in which the patients denied having had rash of miliaria; approximately 25% still had symptoms or signs of miliaria on admission	Present but not severe	No response on anhidrotic areas	Axillary and inguinal in 60%; axillary or inguinal in ?%	Duration of illness: some weeks; insomnia uncommon and due only to itch

anhidrosis.[16] General symptoms were present for an average of two to three weeks before the patients reported ill. It is of interest that anhidrotic asthenia developed in 1 subject within two months of his arrival in the tropics; the mean period was eight and a half months.

Apart from the main symptoms given in table 1, certain less common symptoms may have physiologic relevance. In 4 cases there were swelling and subjective tightness in the hands, particularly in the fingers (intracutaneous edema?).[17] Nosebleed was noticed in 1 case and in another some tenderness of the inguinal lymph glands after exercise. Paresthesias of the extremities were rarely present and never severe. Signs of congestive heart failure were not seen. In no instance was there any evidence of dehydration or of abnormal thirst. As contrasted with those with the congenital disease, few subjects learned to moisten their clothes to obtain a degree of relief.

Observations on the blood pressure before, during and after exercise were not sufficiently detailed to warrant the statement that it is significantly altered as compared with that in normal controls. Clearly, many observations would be required for the compilation of reliable figures. In a few experiments I found that the blood pressure immediately after exercise showed no gross alteration when compared with the same subject's resting level. It is possible that this finding is an abnormality in itself, as a rise in company with exercise is expected. On the other hand, Sulzberger and others[12] noted a substantial rise in the systolic blood pressure immediately after exertion. Although no figures are available, it is presumed that the blood pressure falls dramatically in the rare instances of fainting. The findings of Ladell and others in relation to blood pressure will be given later when their work is discussed.

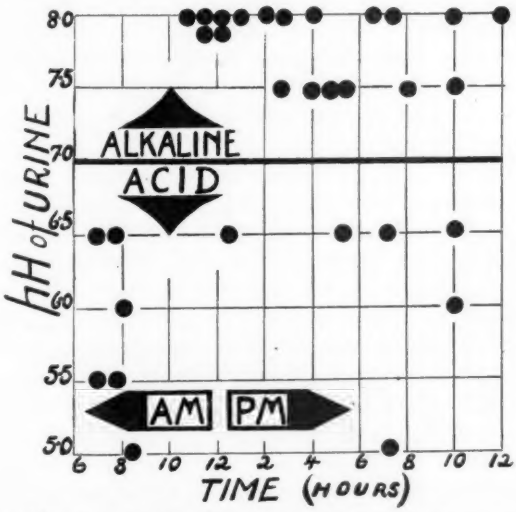
Many subjects had an eosinophilic leukocytosis in the apparent absence of an accepted cause. However, in a few no eosinophilia was present, and as the observations were not sufficiently extended no conclusions can be drawn. Nevertheless, it is worth recording that eosinophils are frequently found in good numbers in sections of skin affected by tropical anhidrosis. It would be of much interest if the various sequelae of miliaria could be proved to be causes of eosinophilia in the tropics.

As regards the physiologic disturbance in anhidrotic asthenia, it can be presumed that the anhidrosis leads to a diminution in the fluid loss from the skin and to an associated change in fluid balance. Although no

16. The duration of the preceding anhidrosis was noted by Ladell and others[5] to vary in the desert from "many days" to three weeks.

17. It is of interest that L. W. Eichna, W. B. Bean, W. F. Ashe and N. Nelson, (Performance in Relation to Environmental Temperature: Reactions of Normal Young Men to Hot, Humid [Simulated Jungle] Environment, Bull. Johns Hopkins Hosp. **76**:25 [Jan.] 1945) record swelling of the hands in normal subjects under heat stress.

precise work was possible under service conditions, it is thought that most of the fluid adjustments take place in the early stages of the disease before advice is sought. However, some polyuria may continue after the patients report ill. Allen[18] found that the average daily fluid intake (exclusive of that in solid food) in 2 cases observed over six days was 1,800 cc. The corresponding urinary output was 1,680 cc. In 1 of these cases the average specific gravity of single specimens collected over the same six days was only 1.009. The relatively large volume and low



Tropical anhidrotic asthenia. The diurnal variation in the reaction of urine passed, over a period of six days, by a resting hospital patient. The large number of p_H readings at or above 7.5 during the heat of the day is noteworthy. (The p_H is estimated by a range of indicators.)

specific gravity of the urine[19] indicate that more fluid than normal was lost by way of the kidneys. Further, the small difference between the fluid intake and the urinary output confirms the curtailment of fluid losses through the skin.

In Ladell, Waterlow and Hudson's[5] cases more obvious polyuria and frequency occurred. They found an average daily urinary output of 2,724 cc.; 2 patients excreted 8,000 cc. per day. When these figures are compared with Allen's, it should be remembered that the degree of polyuria depends not only on the diminution of one avenue of water excretion by the anhidrosis but also on the individual patient's fluid

18. Allen, S. D.: Personal communication to the author.

19. The average normal daily volume of the urine in the humid tropics is 500 to 1,000 cc., figures toward the lower range being more common. Figures for specific gravity below 1.015 are not expected.

intake. According to the intake figures given by Ladell and his colleagues (an average of 7,000 cc. per day), it would seem that their patients maintained a considerably higher intake than is common in the humid zones. I doubt whether many soldiers in the South West Pacific voluntarily maintained an intake of anything like 7,000 cc. per day. This agrees with the usual belief that fluid losses and thus fluid requirements are greater in an equivalent dry climate.[20] It would therefore seem that this apparent difference in polyuria is largely, if not wholly, explicable on the basis of different levels of fluid intake.[21]

Sulzberger and his colleagues[12] give a chart on the fluid, salt and nitrogen balance in their case. Their figures, when compared with those found for normal controls, lead them to suggest that their patient lost as much sweat from his hyperhidrotic areas as the controls lost from their whole bodies. However, as their figures for fluid balance differ from those of other observers, this suggestion should not be accepted as applying generally.

Allen[18] has made some interesting observations on the reaction of the urine; his readings for one typical case are given in figure 1. The patient was at almost complete rest. It will be seen that under such conditions there is evidence of alkalosis during the heat of the day.

The mode of the production of the symptoms and signs of the disease is a subject for speculation. That the anhidrosis is basically responsible can hardly be denied; the means by which it leads to pathologic changes, such as the extreme dyspnea and tachycardia on exertion, is another matter. Various factors probably play a part, and it is thought that the explanation is complex. It can perhaps be presumed that the diminished secretion of sweat onto the cutaneous surface as a whole leads to diminished heat loss and consequent heat retention. But the resulting pyrexia is surprisingly slight and hardly enough to cause much distress on its own account. Further, when the clothes are damped with water to substitute for the absent sweat, the syndrome is still evoked by exercise, though in my opinion it is thereby delayed in its onset and is less severe.

The dyspnea and tachycardia lead one to believe that the circulation of the blood is disturbed. In the absence of any evidence that the heart itself is abnormal, emphasis is naturally placed on an abnormality of distribution of the blood. It seems more than likely that the effective

20. Lee, D. H. K.: A Basis for the Study of Man's Reaction to Tropical Climates, University of Queensland Papers, Department of Physiology, 1940, vol. 1, no. 5, p. 15.

21. Alkalosis can cause diuresis (Bazett, H. C.: Studies on the Effects of Baths on Man: Relationship Between the Effects Produced and the Temperature of the Bath, Am. J. Physiol. 70:412 [Oct.] 1924). However, such an effect is probably not significant in the disease under discussion.

blood volume is diminished by excessive dilatation of the peripheral vessels to such an extent that the circulation cannot meet the needs of both muscles and skin during exercise. In conformity with this view is the general congestion seen in tissue sections. Clinically, however, there is little or no erythema, the congestion being obscured by the whitish anhidrotic vesicles and the generalized edema of the skin. If severe miliaria is still present, the skin is obviously red.

As concerns the presumed peripheral circulatory failure, it is significant that Dill[22] postulated the same concept in regard to the fatigue responses of subjects working in impervious clothing, conditions which are tantamount to those of intrinsic anhidrosis.

In previous papers (Allen and O'Brien,[6] O'Brien[7]) it has been suggested that sweat is reabsorbed into the blood from the anhidrotic vesicles in amounts which are probably considerable and that this resorption may in some way contribute to the production of the abnormal effect of exercise. Sulzberger and others[12] have rightly criticized this suggestion in so far as exercise produces a similar clinical picture in those suffering from a congenital absence of the sweat glands. Nevertheless, the "internal circulation of sweat" is an interesting phenomenon and should not be forgotten in any discussion of the abnormal physiology. Experiments designed to evaluate the possible toxicity of sweat would be of interest in this connection.

It was at one time thought that the hyperpnea might represent a true panting response, a compensatory device enabling a greater loss of water, and thereby heat, via the respiratory system. This suggestion that a change to the canine method of losing heat occurs is intriguing and has been postulated before in explanation of the tachypnea in extreme experimental overheating.[23] In less severe conditions the response is not elicited.[24] Certainly no direct evidence in its favor has been forthcoming in this particular disease. If the hyperpnea were a panting effect some clinical alkalosis might be expected, but in the present cases no evidence of tetany, overt or latent, no definite paresthesias, no carpopedal spasms and no positive Trousseau or Chvostek sign has been demonstrated.

Ladell's[5] Iraq cases afford the most suggestive indication of possible latent tetany; 8 of 55 patients complained of numbness and tingling in the limbs. But such evidence on its own is hardly convincing, especially as tetany due to hyperventilation is possible, as an incidental phenomenon, under any conditions of stress. For instance, frank tetany can

22. Dill, D. B.: The Economy of Muscular Exercise, Physiol. Rev. **16**:263 (April) 1936.

23. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 954.

24. Lee,[20] p. 29.

occur in classic heat exhaustion.[25] Unfortunately the conditions under which the present work was carried out did not allow any chemical examinations to be made. Ladell and others in their studies of anhidrotic asthenia found no definite changes in the blood acid-base equilibrium, but they themselves stated that their observations were not sufficiently exhaustive to justify a final decision on this point.

Sulzberger and his co-workers[12] have recently responsored the idea that an alkalosis due to panting is the direct cause of some of the symptoms and signs, and they specifically cited the dizziness and fainting. They offered support in the demonstration of a fall in the serum content of combined carbon dioxide during static exposure to heat. However, they failed to find an associated change in the blood p_H, though their figures for p_H were persistently at the top of the normal range (7.50). Moreover, they, like other workers, failed to find any clinical sign of even latent tetany. It is perhaps reasonable to expect a fall in the combined carbon dioxide content of the blood in association with the abnormal hyperpnea. However, there is as yet no adequate reason to suppose that any secondary acid-base changes in the blood are habitually uncompensated to a significant degree. Indeed, a further point to be considered in particular relation to exercise is that the acid metabolites produced during muscular activity must tend to counteract any incipient alkalosis due to heat. If, as is thought, a relative deficiency of circulation occurs during exercise, a simultaneous excessive acidosis due to anoxemia is theoretically possible. Clearly there is much scope for inquiry into the acid-base balance of these subjects during both work and rest in heat.

Even if frank tetany regularly occurred during exercise, there still remains the more fundamental doubt that the hyperpnea is a true panting response. Although convenient, such a concept surely exaggerates the sequence of events into a semiphysiologic "mechanism" whose supposed function is to make up for the failure of the skin by an increase in the respiratory heat loss. To give the hyperpnea such a high and complex status seems presumptuous at this stage, particularly when a circulatory disturbance could be a simpler and more direct cause. Moreover, it should not be forgotten that the breathing is not of the shallow panting type. In any case, the suggestion by Sulzberger and his colleagues that an efficacious method of respiratory heat loss exists is contradicted by their own figures for water balance, which indicate, rather unexpectedly, that little or no extra water (and therefore heat) is lost from the respiratory system in tropical anhidrotic asthenia.[26]

25. MacLean, K. S.: Observations on Sunstroke and Heat Exhaustion in the Tropics, J. Roy. Nav. M. Serv. **29**:31 (Jan.) 1943.

26. As a matter of interest, F. W. Sunderman (Persons Lacking Sweat Glands: Hereditary Ectodermal Dysplasia of Anhidrotic Type, Arch. Int. Med. **67**:846 [April] 1941) obtained similar results when studying water balance in the congenital type of the disease.

To conclude this discussion on the proposed role of alkalosis in anhidrotic asthenia, some work of Rice and Steinhaus[27] may be interesting if not fully applicable. In the knowledge that the dog differs from normal man in being prone, when overheated by strenuous work, to an alkalosis from panting, they showed that if the dog is exercised by swimming in water which is sufficiently cool to prevent overheating true panting no longer occurs. What is significant is that the dog's acid-base balance then comes to resemble closely that of man in that acidotic tendencies predominate. The converse possibility therefore suggests itself, i.e., does man, when rendered anhidrotic like the dog, come to share that animal's normal panting and alkalotic reactions? In the formulation of an answer, it is worth recalling that whereas tetany is prone to develop in normal man during overbreathing not once has it been seen as a complication of anhidrotic asthenia.

Ladell and others do not discuss the question of alkalosis, and it is likely that they too thought it unimportant. They simply propose that the respiratory distress of anhidrotic asthenia is due to the stimulating effect of a raised blood temperature on the respiratory center. Even this suggestion is not entirely acceptable in so far as no such gross distress is produced by exercise in otherwise normal subjects whose temperatures are raised to the same degree by some form of toxemia. This is not to deny that pyrexia stimulates the respiratory center; what has to be explained is the severe dyspnea which these anhidrotic patients experience on moderate exertion. The demonstration by Bazett and Haldane[28] and by Landis, Long, Dunn, Jackson and Meyer[29] that the respiratory minute volume during hot bath experiments depends not only on the height of the body temperature but also on the rate of its increase may help to explain the discrepancy. During activity, the temperature of anhidrotic subjects can climb by as much as 2 degrees F. (1.1 degrees C.) within a few minutes.

Relevant to the pyrexia of anhidrotic asthenia is the debatable question of the "normal" upper limit of body temperature in the tropics. In this regard the study of Renbourn and Bonsall[30] on residents of Northern India is of interest, for figures on the order of 101 F. (38.3 C.)

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27. Rice, H. A., and Steinhaus, A. H.: Studies in the Physiology of Exercise: V. Acid-Base Changes in the Serum of Exercised Dogs, Am. J. Physiol. **96**:529 (March) 1931.

28. Bazett, H. C., and Haldane, J. B. S.: Some Effects of Hot Baths on Man, J. Physiol. **55**:iv (March) 1921.

29. Landis, E. M.; Long, W. L.; Dunn, J. W.; Jackson, C. L., and Meyer, V.: Studies on the Effects of Baths on Man: III. Effects of Hot Baths on Respiration, Blood and Urine, Am. J. Physiol. **76**:35 (March) 1926.

30. Renbourn, E. T., and Bonsall, F. F.: Observations on Normal Body Temperatures in North India, Brit. M. J. **1**:909 (June 15) 1946.

for the rectal temperature were often recorded. Likewise, wharf laborers in the tropics can show similar grades of pyrexia (Breinl).[31] However, it must be conceded that the heating effect of miliaria of varying degrees of severity was either not specifically or not completely taken into account in these two studies. Nevertheless, even in laboratory experiments in which the presence of miliaria can be excluded normal acclimatized subjects commonly show temperatures on the order of 101 F. after exercise tests. In fact, Eichna, Ashe, Bean and Shelley[32] inferred that 101 F. should be regarded as the normal upper limit of physiologic response to work in heat. It would thus seem that in anhidrotic asthenia exhaustion ensues during work before the temperature climbs to a striking level and that therefore the pyrexia per se does little to explain the symptomatology.

LITERATURE ON ANHIDROSIS IN RELATION TO HEAT DISORDERS

There exist many accounts of subjects with a congenital absence of the sweat glands, their disease usually being called hereditary ectodermal dysplasia of anhidrotic type. The symptoms and signs which these persons show when exposed to heat are similar to those of the acquired disease described in this paper. For instance, Thannhauser's[33] patient suffered from exhaustion, palpitation, dyspnea and tremor. Sunderman's[34] 3 patients complained of headache and "fever" and showed hyperpnea, tachycardia and diuresis when exposed to high temperatures. It is interesting that the highest oral temperature which Sunderman recorded was only 102 F. (38.9 C.), a temperature comparable with that found in cases of anhidrotic asthenia. However, Hiebert and Garland[35] found that the temperature of the skin was abnormally high; in a child patient it was as high as that found in a normal child with an internal temperature of 104.5 F. (40.3 C.).

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31. Breinl, A.: An Inquiry into the Effect of High Wet Bulb Temperatures upon the Pulse Rate, Rectal Temperature, Skin-Shirt Temperature and Blood Pressure of Wharf Labourers in North Queensland, M. J. Australia **1**:303 (April 16) 1921.

32. Eichna, L. W.; Ashe, W. F.; Bean, W. B., and Shelley, W. B.: The Upper Limits of Environmental Heat and Humidity Tolerated by Acclimatized Men Working in Hot Environments, J. Indust. Hyg. & Toxicol. **27**:59 (March) 1945.

33. Thannhauser, S. J.: Hereditary Ectoderman Dysplasia of the "Anhydrotic Type," with Symptoms of Adrenal Medulla Insufficiency and with Abnormalities of Bones of Skull, J.A.M.A. **106**:908 (March 14) 1936.

34. Sunderman, F. W.: Persons Lacking Sweat Glands: Hereditary Ectodermal Dysplasia of Anhidrotic Type, Arch. Int. Med. **67**:846 (April) 1941.

35. Hiebert, J. M., and Garland, J.: Hereditary Ectodermal Dysplasia of Anhidrotic Type, New England J. Med. **210**:84 (April) 1934.

In other accounts, for instance in MacQuaide's,[36] there is mention of fainting on exposure to the sun. These subjects habitually avoid exposure or work in the heat, and they typically wet their clothes or bathe frequently in order to ameliorate their symptoms in hot weather. One such patient of de Silva's[37] bathed more than twenty times a day.

The skin in these cases of congenital disease is not only dry but also thin, glossy, pliable, somewhat wrinkled and transparent. From the descriptions, it is apparent that neither a miliarial nor an anhidrotic rash is present; this observation tallies with the complete absence of eccrine sweat glands and their ducts in tissue sections. Microscopically, the sebaceous glands and hairs may also be absent.

There is an account by Fog[38] of a young Dane in whom a diffuse anhidrosis developed after paratyphoid. The symptoms were inability to work in the sun associated with a feeling of excessive heat, dull pain in the precordium, palpitation, dyspnea, polyuria and, unlike most typical cases of anhidrotic asthenia, painful paresthesias of the limbs and face. The skin was "dry and scaly." There is no note of preceding or concurrent miliaria. Fog believed that the anhidrosis originated in the central nervous system, but a reading of his paper suggests that despite the long history (six years till the time of examination) the disease was caused by a peripheral obstruction of the sweat glands analogous to that in tropical anhidrotic asthenia.

Fog studied his case fully, and his observations seem pertinent to the tropical disease. When the patient was placed in a hot chamber, a condition thought to be circulatory insufficiency developed. Rales appeared in the lungs, a feature which no other author has noted. More typical of tropical anhidrotic asthenia is that the clothed subject showed a pulse rate of 185 beats and a respiratory rate of 55 excursions a minute while he was undergoing an ergometer experiment of only mild severity under moderate atmospheric conditions. However, in spite of extreme subjective distress, his temperature rose only 0.1 degree C. (0.2 degree F.). Also possibly significant in relation to tropical anhidrotic asthenia is the observation that at about the time the symptoms and signs began the blood pressure fell, despite the continuance of the exertion, to approximately the preexercise level. The subject could work much more efficiently provided he wore scanty clothing and the surrounding air was kept moving by a fan. Fog concluded that the

36. MacQuaide, D. H. G.: Congenital Absence of Sweat Glands, Lancet **2**:531 (Oct. 21) 1944.

37. de Silva, P. C. C.: Hereditary Ectodermal Dysplasia of Anhydrotic Type, Quart. J. Med. **8**:97 (April) 1939.

38. Fog, M.: General Acquired Anhidrosis: Report of a Case and Investigations of the Heat Regulation and Circulation, J.A.M.A. **107**:2040 (Dec. 19) 1936.

heart was not responsible for the circulatory upset, and he placed stress on a peripheral dilatation of the vessels, a general conclusion which, as has been noted, seems to apply to tropical anhidrotic asthenia.

Engelhardt and Melvin[39] described a rather similar instance involving an American white woman aged 49 who had had anhidrosis with lowered heat tolerance for sixteen years. The only preceding disease was typhoid in her youth. At the time of examination she had a red papular rash on the legs which, although not fully described, may have been of a miliarial nature. The photomicrograph of a skin section is not easy to interpret, but it seems to suggest the presence of a keratin plug similar to those described in cases of tropical anhidrosis and anhidrotic asthenia.[7]

In the two accounts just cited there is no indication whether the anhidrosis was confined to the covered parts, as in tropical anhidrotic asthenia, or whether anhidrotic rashes were present. However, a letter by Blank[40] in response to the paper of Wolkin and others[4] implies that genuine tropical anhidrotic asthenia has been observed at times among civilians in the United States of America.

As contrasted with these few accounts of the acquired disease in the subtropical zones, reports are much more definite in their incrimination of anhidrosis as a common and notable cause of failure of heat adaptation in the tropics. However, until the recent war no clear account of anhidrotic asthenia as distinct from the other heat disorders appeared to exist. Except as an acute symptom in cases of actual heat hyperpyrexia, the role of anhidrosis is mentioned rather obliquely or in passing. The association of failure of adaptation with the anhidrosis produced by miliaria is certainly not stressed in any account that I can find. The most suggestive prewar paper is that of Hamilton, Basu and van Haeften[41] who found that of 20 subjects suffering from the effects of heat in Allahabad, 6 had anhidrosis of considerable duration associated with subacute general symptoms such as headache and giddiness. The most significant statement about these 6 patients is that their skins were dry and "sandy" to the touch. Although it is not much to base an opinion on, this "sandy" texture of the skin could easily have been an anhidrotic rash. The authors stated that the 6 patients were always on the verge of heat hyperpyrexia. More will be said about this last comment and of heat hyperpyrexia later.

39. Engelhardt, H. T., and Melvin, J. P.: General Acquired Anhidrosis, Am. J. M. Sc. **210**:323 (Sept.) 1945.

40. Blank, H.: Anhidrosis Following Exposure to Extreme Heat, J.A.M.A. **124**:1152 (April 15) 1944.

41. Hamilton, C. S. P.; Basu, D. N., and van Haeften, J.: Review of Cases of "Effects of Heat" (Heat Stroke, Anidrosis and Heat Exhaustion) Occurring During the Hot Weather of 1929 at Allahabad, J. Roy. Army M. Corps **55**:120 (Aug.) 1930.

The findings of all observers in the recent war are summarized in table 1.[42] The likeness of the conditions described is so great that there appears sufficient evidence to conclude that all are one and the same. At all events, it is justified to assume this as a basis for future work. The points of mutual agreement are so numerous and obvious that only the significant differences call for critical discussion. As a measure of convenience, the name anhidrotic asthenia will be used henceforth to describe the disease as observed by all writers. Later on the merits of the various proposed names will be analyzed.

Wolkin and others[4] gave a description of 8 soldiers who became affected in the American desert area. This team is the only one to stress the existence of a period of generalized hyperhidrosis (excessive sweating) prior to the onset of the cessation of sweating. It is probably unwise to accept this conclusion without reserve. In the first place it is always hard to decide, even on close examination, when free sweating becomes excessive enough to justify the term "hyperhidrosis." There is a normal wide range of secretory power among persons subjected to the same conditions, and some healthy persons sweat extremely freely. Moreover, I have found that patients' statements on their sweat function are untrustworthy and that even intelligent people tend to pay little attention to this aspect of health. Furthermore, the profuse head sweating which develops in anhidrotic asthenia simultaneously as the rest of the body becomes dry often deludes the patients into believing that the whole body sweats intensely. All observers agree that excessive sweating does in fact occur from the face and forehead during the course of the disease, but I have not observed to my satisfaction an unequivocal, general hyperhidrosis preceding the anhidrotic phase, and, as suggested, there is doubt as to the criteria which enable such a hyperhidrosis to be either defined or assessed.

This question of a preceding general hyperhidrosis is not academic, as Wolkin and others go on to argue that the excessive function involved may be thought of as overtaxing the sweat mechanism to the extent of producing a "temporary functional paralysis." Indeed, this is their opinion as to the origin of the anhidrosis. Apart from the doubt that a general preliminary hyperhidrosis does occur and that it can exhaust the sweat function, no direct evidence is available that the sweat mechanism is actually paralyzed in anhidrotic asthenia. Such evidence as is available[7] is in favor of an entirely different concept, namely, that the glands, despite some dilatation, are active and that the sweat produced is unable to reach the cutaneous surface simply because of organic obstructions (keratin plugs) at the sweat pores on the covered parts of

42. Whereas R. G. Park (Disorders Due to Heat, New Zealand M. J. **44**:128 [June] 1945) fully recognizes the general importance of anhidrosis in the tropics, he does not define the entity under discussion.

the skin. It is of course possible, and this is not the point under dispute, that sweating may play a role in causing the fundamental preceding blockage of the pores, that is, the primary histologic lesion of the antecedent miliaria.[7]

In all Wolkin's cases the condition seemed to begin comparatively suddenly, the whole disease coming on over only a few days. Even if this observation is correct and needs no modification from the knowledge that, until the subject works, the disease can be latent, the speed of onset of symptoms is not regarded as a point of fundamental distinction; the malady is essentially the same whether the pores close concurrently or progressively. In all the 8 cases reported by Wolkin and others the disease was severe; indeed, it was apparently by means of its severity that the disease was readily segregated from other heat disorders. If these writers had found and studied cases of less severity, and they inferred that some probably occurred within their available clinical material, they would perhaps agree that in many instances the disease tends to be subacute in its onset, the subject hardly knowing when he first becomes ill. It is, of course, possible that the disease may actually begin more suddenly in the desert than in the humid climate. This is a point which is difficult to elucidate, but I believe that if there is such a true difference it is bound up with a corresponding more fundamental difference in the nature of miliaria in the two climates. In this regard, Wolkin and his co-workers did not observe the etiologic role of miliaria; they noted without comment a history of miliaria some ten days before in their case 5. Yet, credit must go to them for emphasizing the importance of the anhidrotic skin. All their subjects almost certainly had the anhidrotic rash which is now known to be conclusive evidence of antecedent miliaria.[7] In a description of the rash, they mentioned its most striking feature, i.e., its superficial similarity to goose flesh. However, they do not comment on its production by heat and exertion and its disappearance on cooling. It is worth pointing out that these observers say little of local cutaneous symptoms. This corroborates the point that the distressing pruritus of miliaria has nearly always passed away by the time general symptoms arise. An alternative explanation is that the authors may have felt that the presence or absence of miliaria was not worth comment. It is not certain from their account whether the specialized sweat glands of palms and soles, axillas and groin were out of action in their material.

Under the name "heat exhaustion, type II, Ladell, Waterlow and Hudson[5] describe fully, and to some extent in a complementary way, the syndrome as they saw it among troops in the desert of Southern Iraq. The disease, which lasted some ten to twenty days, occurred chiefly toward the end of the summer, when the worst weather was over and cases of the classic heat disorders were no longer frequent. I also

have noted a similar association with the end of the wet season in the humid zones and believe it is due to the fact that miliaria is mild or absent in the early hot weather but gradually increases in severity and incidence with the progress of the season.

In general, the disease as found in the desert by these observers was identical, except for minor variations, with that described herein. In 80 per cent of cases there was a history of moderately severe or severe miliaria a short time previously. Moreover, 87 per cent of the patients gave a history of defective sweating. On examination, the covered parts of the skin were classified as "dry" in 40 per cent of cases. This is a much lower proportion than that found in my own work (all cases), and hardly tallies with their own note of a history of defective sweating in 87 per cent. I suggest that had a starch-iodine or similar preparation been used more than 40 per cent of their patients would have been found to have a significantly large proportion of sweat pores blocked. It should be realized that one difficulty in assessing the presence of an incomplete anhidrosis of the covered parts is that any remaining unaffected sweat glands secrete vigorously and thereby mask the presence of even numerous blocked glands. Therefore, in cases with incomplete dryness one should either perform a starch-iodine or similar test or, as has been suggested,[7] simply estimate the density of the various pore lesions on the skin as a whole after exercise; every anhidrotic vesicle, miliarial vesicle and papule indicates a corresponding obstructed sweat gland.

Ladell and others do not record seeing the anhidrotic rash. Indeed, in a more recent note Waterlow[43] stated that it was definitely not present. As much importance is attached to the changes in the skin for diagnostic and other reasons, this lack of correlation deserves comment. It is noteworthy that Wolkin and others describe the presence of the rash in their cases, which like Ladell, Waterlow and Hudson's, occurred in a dry climate. The latter seem to have given a partial description of such changes when they mentioned the presence of miliaria in the "chronic, healing, desquamating" stage, with "lichenification." In the humid zone this is precisely the stage of miliaria which is associated with the production of the anhidrotic rash on exertion. I feel that this lack of agreement between Ladell's team and other writers resides more in terms than in reality and that the former actually saw the anhidrotic rash but preferred to call it "healing prickly heat." However, it must be conceded that this disagreement may possibly be explicable on other bases. Perhaps Ladell and his colleagues did not exercise their subjects sufficiently before they observed their skins. Perhaps they saw the rash but ignored it because of its similarity to the commonplace goose flesh. Again, general symptoms may ensue in the desert when the miliaria is in a more

43. Waterlow, J., in Allen, S. D., and O'Brien, J. P.: Tropical Anidrotic Asthenia: A Preliminary Report, Bull. War Med. 5:486 (April) 1945.

acute stage, in which case it is proposed that these authors would have seen the development of the anhidrotic rash if they had watched their subjects for a longer period during the skin-healing phase.

That an earlier onset of general symptoms, relative to the stage of the cutaneous lesions, may be the true explanation of the disparity is supported by Ladell's note that 80 per cent of his patients had a still recognizable miliaria. In my experience in the humid zones, and incidentally in Wolkin's in the desert, the cutaneous rash had progressed so fully to the anhidrotic stage that its miliarial origin was by no means obvious and had to be proved by the detailed clinical and histologic work reported elsewhere.[7] There is the final possibility that desert miliaria follows a different course or is a significantly different disease from the variety in the humid areas. I have no experience of the former, so that I cannot base an opinion on direct observation. However, it does seem that such an assumption would, in the present state of our knowledge, complicate matters still further. An examination of published reports does not indicate that a useful purpose would be served at this stage by maintaining that two different diseases masquerade under the name "miliaria rubra." It would appear from the literature that miliaria leads to anhidrosis in the desert just as certainly and in the same way as it does in the humid zones. This is surely the main issue beside which all others fade into insignificance. Slight differences in miliaria as it occurs in the two climates may be admitted; for instance, according to Ladell's account, postmiliarial desquamation is relatively more obvious in the desert zones.

The highest rectal temperature found by Ladell and others was 100.9 F. (38.3 C.), a figure which is consistent with all those already cited. The skin temperatures were relatively high, as was suspected in the earliest observations;[6] for instance, the dry skin of a patient registered a temperature of 100 F. (37.8 C.), while under the same conditions the sweating skin of a control (who incidentally had a mild local miliaria) gave a reading of 95.1 F. (35.1 C.). In hot chamber experiments the rectum-skin temperature gradient was decreased as compared with that in controls. The elevated temperature of the skin can be presumed to be mainly due to a lack of cooling in the absence of effective sweating.

Some observations were carried out by Ladell and others on the blood pressure though not on any changes produced by exercise. The average systolic blood pressure of recumbent patients was 20 mm. higher than that in normal controls, and the pulse pressure was raised. The diastolic pressure varied greatly, being persistently low (40 to 50 mm.) only in some cases. Capillary pulsation was frequently seen (it has not been remarked on in the humid zones). The capillary pulsation

and the increased pulse pressure are consistent with a greatly increased blood flow to the skin. The increased systolic blood pressure, which was apparently more constant than a diminished diastolic pressure, is likely to be due to increased force of venrticular contraction.

There is mutual agreement between all observers that dehydration does not occur in tropical anhidrotic asthenia, and in my view there is little or no evidence of a true deficiency of sodium chloride. In crude testing of the urine, sodium chloride was consistently present in Allen's[18] cases. Ladell and others found that although the chloride concentration in the urine was reduced (presumably due to the diuresis), the total daily chloride excretion averaged 3.47 Gm. (as sodium chloride). Added salt given to a test group was not retained and was excreted at once in the urine, this observation supporting the absence of a true deficit of sodium chloride. The routine chloride intake of these patients was not definitely noted but was apparently in excess of 20 Gm. per day.[44] In groups of fit men on an intake of the same amount the urinary chloride output varied between 3 and 6 Gm. depending on the weather. The Iraq team also found that the extra salt given to half of their patients did not increase the rate of gain in weight over that in control cases.

Ladell and his co-workers produced some evidence in favor of a reduction of the chloride level in the blood, particularly in the plasma. On the other hand, Sulzberger and others[12] found that as the combined carbon dioxide content of the serum fell the chloride content showed a slight and perhaps negligible rise. Clearly the blood chloride may be influenced in different ways by several factors, among which are reduction in blood bicarbonate and disordered fluid balance.[45]

Ladell and others emphasized that many of their patients with unclassified effects of heat had some of the symptoms of anhidrotic asthenia. Moreover, they found every gradation between the fully developed disease and mere exhaustion and weakness. Indeed, Waterlow[43] goes so far as to state that this disease was "by far the commonest disability produced by heat in the desert and, although not severe or dangerous, caused great loss of time and efficiency among troops." This forcible summary also expresses my experience in the humid zones, where the disease is almost commonplace if the subacute cases are taken into account. It is suggested that many of the unclassified cases of the effects of heat will be better understood if more attention is given to the state of the sweat function and, in particular, to the presence and extent of

44. These chloride balance figures are in conformity with the high chloride concentration of such sweat as is secreted by these patients.

45. Unfortunately no evidence is available to show that an abnormally high blood volume occurs in this disease. Comparative studies of blood volume, hematocrit values and similar figures would be of interest in this regard.

miliarial and anhidrotic rashes. Classification will continue to be more difficult in areas of dry climate because the other forms of heat disease (heat stroke and classic heat exhaustion) are more prevalent and therefore cause greater confusion in such areas.

Discussing the question of etiology, the Iraq team suggested that as these anhidrotic patients secrete on their sweating areas a sweat of high chloride concentration (averaging 0.53 per cent as sodium chloride) the basis of the perverted sweat function may be "fatigue" of the sweat glands. In other words, they arrived at much the same opinion concerning the cause of the anhidrosis as did Wolkin and others. However, they also noted that in healthy controls as well as in patients with classic heat exhaustion (type I) the chloride concentration of sweat rises with the progress of the hot season. They observed that "normal" controls secrete less sweat at the end of the season than they do at the beginning. I propose, as a basis for future observation, that all these various changes in sweating owe their origin, at least partly, to the progressive blocking of sweat glands in association with miliaria, and I further propose that in all instances the changes in the chloride concentration of the sweat are due to compensatory hyperactivity of the relatively healthy unobstructed glands. For, as such glands are presumably acting to their greatest capacity, they tend to secrete a sweat which involves the least amount of osmotic work, that is, a sweat which has, like plasma, a relatively high content of chlorides.[46] I doubt whether the term "fatigue of the glands" is justified on the available evidence when reference is being made to these various adjustments of sweating in anhidrotic asthenia and in related obstructive states; it could equally well be argued that the chemical changes in the sweat are wholly compensatory because active secretion continues from normal glands in such instances for as long as they remain unblocked by miliaria. At all events, I have not seen in the humid zones an anhidrosis involving skin which appears otherwise normal. That is to say, anhidrosis appears to be always associated with

46. As the sweat chloride concentration normally falls during acclimatization (Dill, D. B.; Hall, F. G., and Edwards, H. T.: Changes in the Composition of Sweat During Acclimitization to Heat, Am. J. Physiol. **123**:412 [Aug.] 1938), these various rises in concentration suggest, on their own face value, a process of "declimatization" which involves even "normal" controls. It is likely that the increased skin and rectal temperatures which accompany miliaria and its sequelae are the basic indicative factors responsible for the associated high sweat chloride concentration, for in their summary of present knowledge R. E. Johnson, G. C. Pitts and F. C. Consolazio (Factors Influencing the Chloride Concentration in Human Sweat, Am. J. Physiol. **141**:575 [June] 1944) have shown that in general the skin and rectal temperatures are the most potent factors controlling the sweat chloride concentration. A rise in either the skin or the rectal temperature results in a rise in the chloride concentration. It is tempting to believe that the rectal temperature, and perhaps the skin temperature, produces this effect by involving an increase in the rate of sweating from individual sweat glands.

obvious obstruction in the form of miliaria, an anhidrotic rash or ichthyosis. As a final point, when the obstruction at the pores in the last two conditions is relieved by the application of a lipid (the lipid response[7]), the glands discharge such a profuse, visible secretion that the idea of the existence of any form of fatigue can hardly be accepted.

Gerking and Robinson[47] have recently investigated this problem of possible fatigue of the sweat glands in normal "acclimatized" subjects. They found that with high rates of sweating in severe heat the sweat secretion diminished in some cases by as much as 80 per cent of the original rate in six hours even though all requirements for fluid and salt were met. These experiments are significant and certainly tend to show that the sweat glands or, more precisely, the sweat mechanism may become fatigued under extreme conditions. On the other hand, these workers did not produce a complete (local or general) anhidrosis by this method, possibly because the subjects could no longer tolerate the conditions. In similar experiments, Kuo, Takahara, Adachi and Saito[48] also failed to observe complete cessation of sweating. Nevertheless, the evidence for a state of relative fatigue produced by such extreme stress is fairly convincing. How else could the fall in the production of sweat be explained? It is perhaps conceivable that some of the pores could become blocked, even during the course of such short experiments; a swelling of the keratin surrounding the sweat pores might suffice. One observation by Gerking and Robinson perhaps supports the concept of activity of a local factor such as blockage of the pores, i.e., the decrease in sweating is greater under humid conditions (when the skin is bathed in sweat) than it is under dry conditions (when the skin is drier). Yet Gerking and Robinson found that moderate rates of sweating can be maintained without diminution; so it seems, on the whole, that local obstruction of the pores during short experiments, at least to a gross degree, is unlikely.

This analysis is made to demonstrate how complicated is the function of sweating. Apart from the debated question of fatigue, not only is it known that water, sodium chloride[49] and an intact nervous system are all required for the free formation of sweat, but the sweat glands themselves need to have completely patent pores. In fact, the sweat mechanism is probably disabled in the tropics more often by a closure of the pore

47. Gerking, S. D., and Robinson, S.: Decline in the Rates of Sweating of Men Working in Severe Heat, Am. J. Physiol. **147**:370 (Oct.) 1946.

48. Kuo, K. W.; Takahara, K.; Adachi, J., and Saito, K.: Sweating with Heat Stroke, J. Orient. Med. **22**:98 (June) 1935.

49. Taylor, H. L.; Henschel, A.; Mickelsen, O., and Keys, A.: The Effect of Sodium Chloride Intake on the Work Performance of Man During Exposure to Dry Heat and Experimental Heat Exhaustion, Am. J. Physiol. **140**:439 (Dec.) 1943.

than by any other means. It is therefore apparent that while short physiologic experiments in temperate climates are helpful great discretion is necessary when applying the results to the more complex conditions of long tropical residence.

To summarize, it is improbable that Gerking and Robinson's experiments on apparent fatigue shed much direct light on the obstructive type of anhidrosis. It is much more feasible that their experiments are relevant to the type of anhidrosis associated with heat stroke, for in the latter condition, soon to be discussed, the evidence is more suggestive of a true intrinsic deficiency or of failure of the sweat mechanism.

OBSERVATIONS ON THE DIAGNOSIS OF ANHIDROTIC ASTHENIA

As far as the humid zones are concerned, anhidrotic asthenia is readily diagnosed providing the subject is given an adequate exercise test in the heat. In the vast majority of cases the typical cutaneous lesions and the associated anhidrosis are so prominent that a confident assessment in each subject can be made. Experience of the fully developed disease facilitates estimation of the loss of adaptation caused by less general blocking of the sweat pores. Need for its differentiation from heat hyperpyrexia and from classic heat exhaustion (Ladell's type I) simply did not arise in the places in which I worked. In fact, I did not see or hear of these classic diseases affecting troops in the South West Pacific; this is not to say that cases did not occur, but at all events they must have been rare.

In the desert, where I have not worked, the problem of diagnosis is clearly more complex. Heat hyperpyrexia and classic heat exhaustion are apparently so prevalent and dramatic that they eclipse anhidrotic asthenia, although, on the evidence of Ladell and his co-workers, there is no reason to doubt that the disease does occur. Moreover, the work of these observers proves that even when other heat disorders are occurring the discrimination between them and cases of anhidrotic asthenia should be fairly readily made. However, it is subacute in its manifestations, and routine inspection of residents as they work affords the most certain method of detecting it.

Broadly speaking, three different types of heat disease, two of which are classic, and the third new, can be differentiated: (1) heat hyperpyrexia (heat stroke), (2) classic heat exhaustion (Ladell's type I) and (3) tropical anhidrotic asthenia (Ladell's heat exhaustion, type II). Heat cramps is not included as a separate entity because it receives no special discussion in this paper. The disorders are analyzed in table 2.

It will be useful to discriminate between the types of anhidrosis which occur in cases of heat disease. I suggest, for reasons already given, that there are two distinct types which may presumably

TABLE 2.—*Typical Features of the Four Main Heat Disorders (When Seen in Pure Form)*

	Coma	Average Body Temperature	Onset of Associated Anhidrosis	Dry Areas	Miliarial and Anhidrotic Rashes	Urine	Cause
Heat Hyperpyrexia (heat or sun stroke)	Present; may be preceded by stupor, mental excitement, twitchings or convulsions	Over 107 F. (41.7 C.) (rectal)	In pure form, sudden (a matter of hours or at most a day or two beforehand)	Whole of body	Not essential; causal relationship likely when rashes are diffuse	Polyuria in early stages, helpful as a warning sign (chlorides present)	Central failure of heat-regulating mechanism due to stress of accommodating to high external temperatures?; sweat glands produce no sweat
Classic heat exhaustion (type 1 of Ladell and others')[8]	Only syncope; coma rare unless subject at the point of death	100.6 F. (38.1 C.) (rectal)	Anhidrosis not a typical feature		Not essential, but these rashes may be present coincidentally; when present must modify the physiologic and clinical picture	Oliguria (chlorides diminished or absent)	Dehydration because of a sodium chloride deficit within body, deficit being due to an excess of loss in sweat over intake; fluid cannot be retained in absence of sufficient salt—thus "salt deficiency dehydration of extracellular type"
Heat cramps		Not altered in uncomplicated cases	Anhidrosis not a typical feature		(Above comment applies)	Chlorides diminished or absent; (change in volume not essential)	Simple sodium chloride deficiency, not necessarily with dehydration, due to low sodium chloride concentration in body fluids
Tropical anhidrotic asthenia (heat exhaustion, type 11, of Ladell and others')[8]	No coma; occasional dimness of vision on exertion; occasional fainting	100.9 F. (38.3 C.) rectally as found by Ladell and others; 100.0 F. (37.8 C.) orally in the present study	At least a few days and usually one or more weeks before	Clothed areas only	One or other or both types of rash always present and severe when looked for after exertion	Polyuria (chlorides present)	Diminished physiologic adaptation to heat due to an obstructive, peripheral form of anhidrosis caused by miliaria; sweat glands still produce a suppressed secretion, which escapes into skin, causing the lesions

Chief authorities consulted were Ladell, Waterlow and Hudson[8]; Taylor, Henschel, Mickelsen and Keys[49]; Nadal, J. W.; Pedersen, S., and Maddock, W. G.: A Comparison Between Dehydration From Salt Loss and Water Deprivation, J. Clin. Investigation **20**: 691 (Nov.) 1941; and Marriott, H. L.: Water and Salt Depletion, Brit. M. J. **1**:245 (Feb. 15), **1**:285 (March 8) and 1:328 (March 15) 1947.

Mixed states in heat disease are the rule. Temperatures over 105F. usually indicate heat hyperpyrexia. Not included in the table are (1) simple heat syncope (fainting) and (2) dehydration due to simple water deficiency.

be intermingled. The anhidrosis of heat hyperpyrexia and perhaps of "threatening" heat hyperpyrexia is usually thought to be of central origin—an intrinsic failure or paralysis of the heat-regulating centers.[48] Consequently, it is suggested that in heat hyperpyrexia the sweat glands receive no stimuli to secrete and therefore produce no sweat. The second is the extrinsic or periphheral obstructive type, namely, tropical (postmiliarial) anhidrosis, in which, by contrast, the glands are active but the sweat they produce cannot reach the cutaneous surface; it is reabsorbed as a suppressed secretion from the dermis.[7] The distinction between the two types is believed to be fundamental.

In Ladell's experience, patients with heat hyperpyrexia stated that sweating ceased suddenly over the entire body from half an hour to three hours before general symptoms began. With recovery, recurrence of sweating was just as rapid. Most accounts, such as that of Hearne,[50] agree on the evanescence of this type of anhidrosis, and in this respect the disease differs strikingly from anhidrotic asthenia. Other characteristic features of heat hyperpyrexia are the stupor and the final coma, the extremely high body temperature and, in many cases, diminished or absent knee jerks. During the stage of incipient heat stroke the warning symptoms which may be present[51] are giddiness, nausea, headache, dyspnea and, above all, generalized anhidrosis and polyuria. It will be noted that all these symptoms, except nausea, are prominent in anhidrotic asthenia. The polyuria, like the casual anhidrosis, comes on more acutely in heat stroke.

Ladell and others agree with the almost universally held opinion that in heat hyperpyrexia there is a true failure of the sweating and heat-regulating mechanisms and that the failure probably originates in the central nervous system.

As regards classic heat exhaustion, the Iraq team pointed out that it occurs chiefly in the hottest weather when the requirements of salt and water are at their maximum. The chief clinical features distinguishing it from anhidrotic asthenia are the severe and constant collapse, with pale skin, low pulse pressure (in 35 per cent of cases), cramps (70 per cent), vomiting and dehydration (50 per cent), oliguria and diminished or absent urinary chloride (73 per cent). The most striking distinction

50. Hearne, K. G.: Hyperpyrexial Heat Stroke: A Mesopotamian Experience with Some Aetiological Views and a Method of Prevention Resulting Therefrom, M. J. Australia **1**:226 (Feb. 13) 1932.

51. Lee,[30] p. 52.

52. Although most writers agree that anhidrosis is not a significant element of classic heat exhaustion, G. H. Collings, L. A. Shoudy and F. E. Shaffer (The Clinical Aspects of Heat Diseases, Indust. Med. **12**:728 [Nov.] 1943) described it as occurring in 26 per cent of a group of patients with exhaustion and cramps. The probability that this proportion may have been in a state of "threatened" heat hyperpyrexia does not seem to have been fully excluded. Neither were the occurrence and the anhidrotic effect of miliaria taken into account.

is the profuse sweating from the skin as a whole.[52] Etiologically, classic exhaustion is regarded by Ladell and others as a manifestation of dehydration secondary to a deficiency of sodium chloride within the body fluids. Peripheral circulatory failure is an important element in the final clinical picture.

It is noteworthy that the internal temperature is not a reliable guide in discriminating between anhidrotic asthenia and heat exhaustion, as in both it is moderately raised. Similarly, headache, giddiness and anorexia may be present in both. On the other hand, the episodes of anhidrotic asthenia are usually more closely associated with exertion, and the symptoms and signs are not as a rule prolonged to any great degree into the postexertional period. Syncope on standing (associated with a rapid, feeble pulse and falling blood pressure), which Ladell and others stress as being so notable in heat exhaustion (73 per cent of cases), is not a prominent feature of anhidrotic asthenia. In the latter, syncope is not common, and, in my experience, is usually precipitated by exercise more strenuous than that of mere standing. Heat exhaustion is curable in a few hours by the use of isotonic sodium chloride solution, and anhidrotic asthenia is not; in cases of the latter an excess of water and salt may possibly be more embarrassing than a deficiency in so far as one of the normal excretory channels (the skin) is largely interrupted.

Although the three listed diseases may occur in a pure form in the dry zones, the Iraq team remarked that the particular clinical picture is frequently complicated by the presence in individual cases of elements of two or more of the syndromes. That this should be so can readily be understood. For if, as is believed, a relatively normal person with previously good sweat function can contract heat hyperpyrexia, it seems only reasonable to postulate that a subject with anhidrosis due to miliaria is, on that account, in even greater danger. Such an association is suggested by Ladell's patients with heat hyperpyrexia, all of whom had some degree of prickly heat on their admission to the hospital, which was, however, "not severe." I would suggest, on the basis of their own remark that only 40 per cent of their subjects with frank anhidrotic asthenia had a dry skin, that Ladell and his co-workers were inclined to underrate the severity of prickly heat in respect to its anhidrotic effect. A relationship between the two diseases is further indicated by one of their cases in which a patient with anhidrotic asthenia had a temperature of 105 F. (40.6 C.), a degree of pyrexia which is not expected in the uncomplicated form of the disease. It is also supported by Wolkin's case 6, in which the extremely rapid onset and disappearance of anhidrosis (apparently complete) suggested the complication of at least some central failure of sweating. It can be presumed that this rather atypical case was included in the series because there was a diffuse anhidrotic rash; in other words, features of both syndromes were seem-

ingly present. Again, Ferris, Blankenhorn, Robinson and Cullen,[53] in a study of 44 patients with heat stroke in the United States of America, found that more than half had, besides a dry skin, a "characteristic maculo-papular skin rash present on the body, being most marked over the chest, abdomen and back. This eruption was fiery red in color and in many areas purpuric." What was this rash if not miliaria complicated by the purpura[54] of heat stroke? Moreover, Morton[55] spoke of a hot dry roughened skin in heat stroke.

It is therefore believed that subjects with miliaria, tropical anhidrosis and anhidrotic asthenia are not immune to heat stroke, and indeed there appears to be good reason to maintain that, owing to their diminished heat tolerance, they are more susceptible than persons who sweat normally. Is it not probable that the compensatory hyperactivity of such glands as escape miliaria may promote the fatigue type of failure as described by Gerking and Robinson?[56] If, as seems likely, further work should prove these views to be correct, miliaria will be credited with a far more vicious status than has hitherto been the case.

It should be pointed out that if heat hyperpyrexia develops in a person with tropical anhidrosis, anhidrotic asthenia or even acute miliaria the associated central paralysis of the sweat mechanism theoretically would lead to the disappearance or at least the amelioration of the characteristic rashes of the conditions, for, as has been shown elsewhere,[7] these rashes owe their origin and continuance to escape of sweat into the tissues of the skin. Therefore, in a case of heat stroke the true state of the skin cannot be correctly estimated until the heat-regulating mechanism recommences its function. The best index of the resumption of the intrinsic activity of the sweat mechanism would be afforded by facial sweating. It can be further presumed that when heat stroke develops in a person with anhidrotic asthenia all areas which were previously sweating, such as the face, become dry. As heat stroke was not encountered during the present study, the suggestions could not be put to a test.

It is also possible that patients with classic heat exhaustion may show some manifestations of tropical (postmiliarial) anhidrosis. For instance, it appears from the account of Ladell and his co-workers that

53. Ferris, E. B.; Blankenhorn, M. A.; Robinson, H. W., and Cullen, G. E.: Heat Stroke: Clinical and Chemical Observations on Forty-Four Cases, J. Clin. Investigation **17**:249 (May) 1938.

54. Wright, D. O.; Reppert, L. B., and Cuttino, J. T.: Purpuric Manifestations of Heat Stroke, Arch. Int. Med. **77**:27 (Jan.) 1946.

55. Morton, T. C.: Heat Effects in British Service Personnel in Iraq, Tr. Roy. Soc. Trop. Med. & Hyg. **37**:347 (May) 1944.

56. This probability is not incompatible with my opinion that in the humid zones a fatigue type of anhidrosis is not responsible for any part of the clinical picture of either tropical (postmiliarial) anhidrosis or anhidrotic asthenia.

some of their subjects with classic heat exhaustion had symptoms which truly belong to tropical anhidrosis, namely, a history of "defective sweating" (13 per cent of cases), "desquamating prickly heat" (7 per cent) and skins classified as "dry" (5 per cent).[57] Conversely, 4 per cent of their patients with anhidrotic asthenia had cramps and vomiting, features normally part of heat exhaustion. These observations certainly favor the idea that mixed states of heat exhaustion and tropical anhidrosis occur.

Nevertheless, providing present etiologic conceptions are correct, fully developed heat exhaustion and fully developed anhidrotic asthenia are perhaps mutually exclusive in so far as a patient with more than a moderate degree of tropical anhidrosis is probably unable to lose enough sodium chloride through the skin to be in danger of heat exhaustion. It is therefore predicted that patients with heat exhaustion are unlikely to show more than a mild degree of tropical (postmiliarial) anhidrosis. Conversely, patients with anhidrotic asthenia are not prone to the salt and water deficiences of heat exhaustion; in particular, cramps, vomiting, oliguria or achlouria are not to be expected. That 4 per cent of Ladell's patients with anhidrotic asthenia did in fact have cramps and vomiting cannot be easily explained on present hypotheses; perhaps in these instances vomiting, which is typically absent or inconspicuous, led to an excessive loss of chloride in the vomitus. Despite all that has been said in this paragraph, there is still scope for an etiologic connection between tropical anhidrosis and classic heat exhaustion. It has already been noted that tropical anhidrosis probably precipitates a rise in the sweat chloride concentration or is associated with it. Should the rise in chloride concentration relatively outstrip the fall in sweat production, then the total loss of chloride from the body could clearly increase. This possible effect of miliaria is well worth study.

Because of its intermittent nature, anhidrotic asthenia is prone to be mistaken for a psychiatric disorder. Confusion arises since those affected say that their inability to work is confined to the middle of the day. The morning sick parade held by the services does not facilitate diagnosis, for at that time the subjects feel well and may show to an unwary eye no evidence of the anhidrosis and rash. However, they give a typical history which, if not conclusive, is at least suggestive. There should be no difficulty when the persons are observed at work. If the cutaneous changes are ignored, simple indolence and the "effort syndrome" (Lewis) are other possible sources of confusion.

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57. From their account, it is unlikely that "threatened" heat stroke could have been responsible for the "defective sweating" and "dry skin" seen in these instances.

INCIDENCE OF MILIARIA AND TROPICAL ANHIDROSIS IN THE FIELD

Inspection of units reveals that severe anhidrotic asthenia, mild anhidrotic asthenia and simple tropical (postmiliarial) anhidrosis are increasingly prevalent in that order. In carrying out such survey work, it is necessary to examine all subjects immediately after exertion. Further, in the estimation of cutaneous changes, it is important to be guided more by the profusion of the various miliarial and anhidrotic lesions than by the presence or absence of patches of complete dryness. My experience with troops was that 35 to 70 per cent had the characteristic cutaneous changes to at least a "moderately severe" degree, the basis for these estimates having been the "severe" involvement of the skin in frank anhidrotic asthenia. The more active units showed the greater incidence. It was thought unwise to resort to the direct elicitation of symptoms on these routine inspections of units; still, it was hard to avoid the conclusion that a large proportion of the men would have been fitter without their anhidrosis. It is unfortunate that the severity of an anhidrosis cannot be easily measured quantitatively; neither can the associated loss of adaptation. In general, one can only be guided by previous knowledge of asthenic patients.

The incidence of moderately severe obstructive anhidrosis (35 to 70 per cent) probably depends on the incidence of miliaria as it varies from one unit to another.[58] As regards general symptoms, I have made the broad tentative suggestion[7] that when half the sweat pores on the covered parts are blocked, there is probably some loss of adaptation and that when two thirds or more are affected, the loss of adaptation is likely to be severe. Precise measurements of the amount and the chloride content of the sweat produced in anhidrotic states of varying intensity would be of much interest.

TERMINDLOGY

The thermal disorder which may follow miliaria is specific enough to merit a name. From the point of view of time of publication, "thermogenic anhidrosis" has priority by a few months. Yet this name is not entirely suitable, for while it has the advantage of stressing the significant role of the anhidrosis, it is defective in the use of the qualification "thermogenic." As a result, the meaning of the combined term is not clear; if it is intended to convey the impression that the high external

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58. In the Merauke climate, Kendall[13] found that 91 per cent of the men in his unit suffered from miliaria at one time or another during a period of ten months. M. B. Sulzberger and L. O. Emik (Studies on Prickly Heat: I. Clinical and Statistical Findings, J. Invest. Derm. 7:53 [Feb.] 1946) found an incidence of 66 per cent during a period of seven months on Guam.

temperature produces the anhidrosis it is open to criticism because present knowledge is against such a relationship in this disease. At best a connection is remote and exists through the mediation of miliaria. "Thermogenic anhidrosis" is also unsatisfactory if it is intended to convey the idea that the anhidrosis produces a dramatic rise in the body temperature. The rise in temperature is almost always slight in the uncomplicated form of the disease; the exhaustion and the other asthenic features are far more noteworthy.

Ladell and others showed reticence in their choice of the term "heat exhaustion, type II." Their paper gives the impression that although they were convinced of the basic role of the anhidrosis they were not prepared to sponsor the association by giving it a name. They once used the term "anhidrotic heat exhaustion," and although this was satisfactory they did not persevere with it. However, as most physicians already have in their minds a concept of classic heat exhaustion, including its cause, it seems a pity to confuse matters now by dividing heat exhaustion into two different clinical and etiologic types, particularly in so far as it is now justifiable to adopt an etiologic name for the "type II."

"Tropical anhidrotic asthenia" appears to get over these difficulties and was chosen after much familiarity with the disease. It is descriptive in that it implies the leading characteristics of the disease, i.e., the anhidrosis, and the combination of asthenic symptoms and signs. Further, the name arose out of the earliest work in the field[6] and has recently been adopted by Sulzberger and others[12] for their contributions.

SUMMARY

In their classic paper on the physiologic and clinical responses of man to the desert, Ladell. Waterlow and Hudson[5] ask: "Is severe prickly heat inevitably or usually followed by general symptoms?" The certain answer, which they help to give, is "inevitably, yes." By involving blockage of the sweat pores, miliaria produces anhidrosis and thereby diminishes heat tolerance. The broad inferences of this simple concept need hardly be stressed.

The heat disease produced by miliaria is subtle and shows little of the urgency and danger to life associated with the familiar syndromes. It is distinguished rather by malaise, a distaste for work and excessive fatigue on physical activity. In other words, it is closely bound up with the subtle problem of incipient loss of acclimatization.

The several accounts from both the wet and the dry zones are re-

markably similar. After arrival in the tropics and a few months of health comes the provoking attack of miliaria. The attack may or may not be severe. After a further but shorter latent period, the patient commences to suffer from asthenic symptoms, exhaustion, headache, dyspnea and giddiness, when working in the heat. When seen after exercise he shows not only gross cardiorespiratory distress but also an anhidrosis on the covered areas and a characteristic anhidrotic (gooseflesh-like) rash. The disease, which has been named tropical anhidrotic asthenia, lasts some weeks and may then pass away as gradually as it came on.

As regards differences between the various accounts, one team's suggestion that the anhidrosis is preceded by a period of generalized, excessive sweating is not supported by the results of close analysis. However, the observation that all unblocked sweat glands hypersecrete during the course of the disease is accepted by all. Another team does not record seeing the anhidrotic rash. This disparity is probably explicable on the basis of terms rather than of objective distinctions.

Why a subject with anhidrosis should suffer from symptoms when exposed to heat poses tantalizing problems. Many factors probably play a part, and different authors stress them in varying degree. One observation which has to be taken into account is that the body temperature typically does not rise as high as might be expected. This is significant, for at least one group of writers emphasizes the stimulating effect of increased blood temperature on the respiratory center. Another team favors the idea that the symptoms and signs arise because of an alkalosis which results from a panting type of compensatory hyperpnea. This hypothesis lacks sufficient clinical evidence, and the available chemical data are merely consistent and not positively supportive. On the other hand, it is proposed in the present paper that while some truth may rest in all these hypotheses most of the clinical response to exercise is probably accounted for by a temporary circulatory failure of peripheral type. The following postulates are reached in a review of the classic heat disorders in the light of present knowledge of anhidrotic asthenia:

1. There are two distinct types of anhidrosis encountered in the tropics. One is associated with heat hyperpyrexia and is thought to be due to an intrinsic, central failure of the sweat mechanism. The other is the peripheral obstructive type associated with miliaria and its sequelae, tropical (postmiliarial) anhidrosis and anhidrotic asthenia.

2. Because it lowers heat tolerance, miliaria probably predisposes toward heat hyperpyrexia. The sequence of events may well be as

follows: miliaria, compensatory hyperactivity of unaffected sweat glands, fatigue or failure of the sweat mechanism and heat hyperpyrexia.

3. By causing a rise in the chloride concentration of sweat, miliaria and its sequelae may, under specified conditions, predispose toward classic heat exhaustion.

4. The presence of any anhidrosis due to miliaria must modify the clinical and pathologic pictures of the classic heat disorders.

NEEDLE BIOPSY OF THE LIVER

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MILWAUKEE

IT HAS been apparent for years that some aid must be found in making an early diagnosis of diseases of the liver, especially when there is minimal or moderate functional impairment. Employment of needle biopsy of the liver has been useful in this regard, and evidence is accumulating which indicates the value of this procedure.

Through the use of the biopsy needle, new light has been shed on some of the problems which have always been difficult to solve diagnostically. This is well illustrated in instances of prolonged jaundice, in which it is imperative to determine whether the cause is intrahepatic or extrahepatic, in order to institute the proper treatment. Another problem frequently encountered is that of portal cirrhosis, the manifestations of which may be overlooked or difficult to evaluate, especially in early cases or in the presence of disease of the heart and/or kidneys. Similarly, the role of enlargement of the liver secondary to a systemic disease, such as diabetes mellitus, thyrotoxicosis, amyloidosis or hemochromatosis, is difficult to determine. Patients suffering from carcinoma of the liver, metastatic or primary, are often subjected to laparotomy because the condition was undiagnosed beforehand.

Experience with one hundred and eleven biopsies of the liver in 100 patients has led us to analyze our results in order to determine the diagnostic value of this measure, to estimate the percentage in which a specimen satisfactory for histologic study may be obtained and to emphasize the indications, contraindications and complications associated with biopsy of the liver.

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REVIEW OF THE LITERATURE

The first recorded biopsy of the liver was performed in 1895 by Lucatello,[1] although puncture of the liver for therapeutic purposes in cases of abscess and hydatid disease had been reported by Biett[2] and Roberts (performed by Stanley[3]) in 1833, Hammond[4] in 1878 and Sims[5] in 1879. Twelve years after Lucatello's original work, Schupfer[6] reported a series of cases of biopsy of the liver. These investigators used a technic consisting of the introduction of a small bore needle into the liver, followed by aspiration of a few fragments of hepatic tissue and blood, which were smeared on a slide, stained and examined. Although this method entails relatively little risk and is said to enable frequent diagnoses, it does not permit a study of architecture and stroma. Frola[7] reviewed the reports of aspiration biopsy of the liver in a monograph published in 1935 and reported 66 cases of his own. Examination of his photomicrographs reveals a few particles of hepatic tissue and blood cells, which demonstrates the limited value of this technic. Despite these handicaps, this method has retained popularity in Europe, as evidenced by a number of reports in recent years.[8]

In 1923, Bingle and Olivet developed a technic which enabled them to obtain a small specimen of hepatic tissue which was satisfactory for the preparation of paraffin sections. Bingel[9] reported 100 cases, with

1. Lucatello, L.: Sulla puntura del fegato a scopo diagnostico, Lavori d. Cong. di med. int. **6**:327-329, 1895.

2. Biett: Hydatides du foie, avec dévelopement considérable de cet organe: Ponction explorative; incision; sortie d'une grande quantité d'acéphalocystes; guérison, Gaz. d. hôp. **7**:383, 1833.

3. Stanley: Cases at St. Bartholomew's Hospital, Lancet **2**:189-190 (Oct. 26) 1833.

4. Hammond, W. A.: Some Points in the Pathology and Treatment of Hepatic Abscesses, St. Louis M. & S. J. **35**:72-76, 1878.

5. Sims, J. M.: Diagnosis of Abscess of the Liver by Symptoms of Cerebral Hyperaemia, with Some Remarks on Treatment of Hepatic Abscess by Aspiration, Tr. M. Soc. Virginia **3**:106-111, 1879.

6. Schupfer, F.: De la possibilité de faire intra vitam un diagnostic histopathologique précis des maladies du foie et de la rate, Semane méd. **27**:229, 1907.

7. Frola, E.: Il puntato epatico nella diagnosi delle malattie del fegato, Rome, Luigi Pozzi, 1935.

8. Huard, P.; Meyer, M. J., and Joyeux, B.: La ponction biopsie du foie et son utilité dans le diagnostic des affections hépatiques, Ann. d'anat. path. **12**:1118-1124 (Dec.) 1935. Fiessinger, N., and Laur, C. M.: L'hépatogramme en clinique courante, in particulier dans le diagnostic du cancer du foie, Sang **12**:102-106, 1938. Weil, P. E.; Isch-Wall, P., and Perles, S.: La ponction du foie dans l'ictère hémolytique, la cirrhose pigmentaire, le cancer mélanique, ibid. **12**:97-102, 1938. Hatieganu, I.; Sparchez, T.; Radu, P., and Macavie, I.: Der Wert der Leberpunktion in der Diagnose der verschiedenen Lebererkrankungen, Wien. klin. Wchnschr. **56**:21 (Jan. 15) 1943.

9. Bingel, A.: Ueber die Parenchympunktion der Leber, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:210-212, 1923.

2 deaths due to hemorrhage, and Olivet[10] in 1926 evidently extended the series, reporting 140 cases, with an additional death due to peritonitis. A modification of their technic, which has been widely used since, was developed by Iversen and Roholm[11] in 1939. These investigators used a cannula 18 cm. long and 2 mm. wide and a pointed stylet. After antiseptic cleansing and anesthesia, this needle is introduced into the ninth intercostal space in the posterior axillary line and inserted into the liver, after passing through the pleural space and the diaphragm, while the patient holds his breath in expiration. The stylet is withdrawn and a record syringe (10 cc.) attached to the cannula. Suction is then applied and the needle forced 1 to 2 cm. farther into the liver while the syringe is rotated. The cannula is then quickly withdrawn and yields a specimen satisfactory for microscopic examination. They reported one hundred and sixty biopsies on 114 patients with this method, with a successful result in 22.5 per cent. Two patients evidenced signs of intraperitoneal hemorrhage, which at autopsy was not thought to have caused death. A further report of eleven biopsies, without complications, of 10 patients, performed in a study of hepatitis, was presented by Roholm and Krarup[12] in 1940. Dible, McMichael and Sherlock[13] in England made a study of epidemic hepatitis, arsenotherapy jaundice and serum jaundice during World War II, using the method of Iversen and Roholm. They reported one hundred and twenty-six punctures of the liver, following which 2 patients had nonfatal hemorrhage, 1 patient had hemorrhage but died of acute necrosis of the liver and 1 patient died of necrosis of the liver and rectal carcinoma and was observed to have blood-stained ascitic fluid at autopsy. This series was apparently extended by Sherlock[14] in 1945 in a report of one hundred and thirty-eight additional biopsies, using the same technic but with a longer and narrower needle. Approximately 6 per cent failure was recorded for the two hundred and

10. Olivet, J.: Diagnostic Puncture of Parenchyma of Liver, Med. Klin. **22**: 1440-1443 (Sept. 17) 1926.

11. Iversen, P., and Roholm, K.: On Aspiration Biopsy of Liver, with Remarks on Its Diagnostic Significance, Acta med. Scandinav. **102**:1-16, 1939. Roholm, K., and Iversen, P.: Changes in Liver in Acute Epidemic Hepatitis (Catarrhal Jaundice) Based on Thirty-Eight Aspiration Biopsies, Acta path. et microbiol. Scandinav. **16**:427-442, 1939.

12. Roholm, K., and Krarup, N. B.: Die Histopathologie der Leber bei sog. Salvarsanikterus, mittels Aspirationsbiopsie untersucht, Arch. f. Dermat. u. Syph. **181**:521-523, 1940.

13. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic, Arsenotheray and Serum Jaundice, Lancet **2**:402-408 (Oct. 2) 1943.

14. Sherlock, S.: Aspiration Liver Biopsy: Technique and Diagnostic Application, Lancet **2**:397-401 (Sept. 29) 1945.

sixty-four biopsies, with no additional complications or fatalities. These authors emphasized that biopsy of the liver should not be performed unless adequate facilities for blood transfusion are available, in the event of hemorrhage. They also stated that the risk of hemorrhage is greatest in severely jaundiced patients, especially if the jaundice is due to acute parenchymatous hepatic disease, and added that they had never observed evidence of hemorrhage in nonjaundiced patients. Van Beek and Haex[15] reported 100 cases of aspiration biopsy of the liver in cases of infectious mononucleosis and benign sarcoid.

Laparoscopic control of biopsy of the liver was reported in one hundred and twenty-three instances by Kalk, Bruhl and Sieke[16] in 1943, with no complications. This method is undoubtedly safer than biopsy with an external approach alone, but it involves the use of the operating room and is time consuming.

In the first report of biopsy of the liver in the United States in 1939, Baron[17] recorded forty-eight aspiration biopsies in 35 patients, several of which were performed intercostally. This technic was abandoned in later cases, because of the potential dangers associated with its use, and an anterior subcostal approach was used. One fatal hemorrhage occurred in this series. Chiray, Fiessinger and Roux[18] also used the anterior subcostal approach in 41 cases reported, in which there was 20 per cent failure. These authors had no untoward results and ascribed this to their having penetrated the liver only to a depth of 3 cm., thus avoiding the large blood vessels. Introduction of the biopsy needle at the apex of the angle between the xiphisternum and the right costal margin was reported by Gillman and Gillman[19] in 1945 in a series of five hundred biopsies of the liver.

A special needle primarily intended for biopsy of tumors was first described by Silverman[20] in 1938. The use of this instrument for

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15. Van Beek, C., and Haex, A.: Aspiration-Biopsy of Liver in Mononucleosis Infectiosa and in Besnier-Boeck-Schaumann's Disease, Acta med. Scandinav. **113**:125-134, 1943.

16. Kalk, H.; Bruhl, W., and Sieke, W.: Deliberate Liver Puncture, Deutsche med. Wchnschr. **69**:679-712 (Oct. 1) 1943; abstracted, J.A.M.A. **128**:157 (May 12) 1945.

17. Baron, E.: Aspirations for Removal of Biopsy Material from the Liver, Arch. Int. Med. **63**:276-289 (Feb.) 1939.

18. Chiray, M.; Fiessinger, N., and Roux, M.: La ponction-biopsie du foie, Presse méd. **49**:785-788 (July 22) 1941.

19. Gillman, T., and Gillman, J.: A Modified Liver Aspiration Biopsy Apparatus and Technique, with Special Reference to Its Clinical Applications as Assessed by Five Hundred Biopsies, South African J. M. Sc. **10**:53-56 (June) 1945.

20. Silvermann, I: A New Biopsy Needle, Am. J. Surg. **40**:671-672 (June) 1938.

biopsy of the liver was recorded in a report of 14 cases in a series of unstated number by Tripoli and Fader[21] in 1941. They recommended the anterior subcostal approach, just to the right of the rectus muscle, where the abdominal wall is thin, and confined their biopsies to patients in whom the liver was palpable. Using the method described by Tripoli and Fader, Hoffbauer[22] in 1945 reported sixty-five biopsies, with no serious hemorrhage. Twenty of these biopsies were performed under peritoneoscopic control, with a modified Vim-Silverman needle, 18 cm. in length. Most of these cases are apparently included in a report by Hoffbauer, Evans and Watson,[23] published in 1945, on a study of cirrhosis of the liver and the correlation of tests of hepatic function with biopsy of the liver. They reported 85 cases, in 15 of which failure occurred (18 per cent) and in 20 of which the technic was carried out in the operating room under peritoneoscopic control. The Vim-Silverman needle was used in all instances, and one severe nonfatal hemorrhage occurred. The authors were not able to correlate the results of studies of hepatic function with the histologic changes in the biopsy specimen of the liver. In 1946, Davis, Scott and Lund[24] reported seventy-nine biopsies, with 86 per cent success, using several instruments, including a large bore needle, the Vim-Silverman needle and the Roth-Turkel needle.[25] There were no fatalities. In commenting on the use of the Roth-Turkel needle, the authors pointed out that while it is larger and yields larger specimens without compression of tissue, it is more difficult to control than the Vim-Silverman needle. Popper, Franklin, Steigmann and Kozoll[26] reported a study in 1946 in which biopsies had been performed on 85 patients. They stated that they were able to correlate accurately the results of some studies of hepatic function and certain pathologic changes, as revealed by histologic changes in the biopsy specimen.

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21. Tripoli, C. J., and Fader, D. E.: Differential Diagnosis of Certain Diseases of Liver by Means of Punch Biopsy, Am. J. Clin. Path. **11**:516-527 (June) 1941.

22. Hoffbauer, F. W.: Needle Biopsy of the Liver, Journal-Lancet **65**:246-248 (July) 1945.

23. Hoffbauer, F. W.; Evans, G. T., and Watson, C. J.: Cirrhosis of Liver Presenting Clinical Features of Xanthomatous Biliary Cirrhosis but with Confirmation at Autopsy (Follow-Up of Case Reported Previously), M. Clin. North America **29**:1054-1055 (July) 1945.

24. Davis, W. D.; Scott, R. W., and Lund, H. Z.: Needle Biopsy of the Liver, Am. J. M. Sc. **212**:449-461 (Oct.) 1946.

25. Roth, A A., and Turkel, H.: Technique of Prostatic Biopsy, J. Urol. **51**:66-68 (Jan.) 1944.

26. Popper, H.; Franklin, M.; Steigmann, F., and Kozoll, D. D.: Relation Between Structural and Functional Alterations of the Liver, Proc. Central Soc. Clin. Research **19**:11-12, 1946.

METHOD AND MATERIALS

From August 1945 to February 1947, we performed one hundred and eleven biopsies of the liver of 100 patients.[27] Of these, 63 were male and 37 were female; 93 were white and 7 were Negro. The ages ranged from 29 to 79 years. The Vim-Silverman needle was used in all instances, and one hundred and seven of the biopsies were performed ante mortem. Ninety-seven biopsies (87.4 per cent) were successful, and fourteen biopsies (12.6 per cent) failed in this series, the latter including those in which too little tissue or no tissue was obtained for study. Failure was due principally to lack of experience in use of the technic, as the last fifty-five biopsies performed were successful. A sharp needle is necessary to obtain a satisfactory core of tissue, and we feel that three of our failures may be attributed to not having had the needle sharpened. Other failures were due to livers being palpable less than 2 cm. below the right costal margin and to cystic disease. The technic used is as follows:

The procedure is performed at the bedside, following the administration of 50 to 100 mg. of meperidine hydrochloride to allay apprehension. After the usual preparation of the skin with iodine and alcohol, a sterile drape is placed over the area selected for biopsy. This may be located at any point where the liver is easily palpable: below the right costal margin in the midclavicular line, in the midline below the xiphoid process or in the right flank. If there are any palpable nodules, an attempt is made to enter one of them. From 4 to 6 cc. of 2 per cent procaine hydrochloride is then infiltrated into the skin and subcutaneous tissues down to and including, if possible, the parietal peritoneum. As a rule, the patient will give some sign when the point of the needle reaches the peritoneum, and an additional 0.5 cc. is injected at this point. In approximately two minutes the anesthetic is effective, and a small incision is made in the skin to facilitate passage of the needle. The needle, with the obturator in place, is then inserted through the anesthetized tract and into the liver for 1 to 2 cm., at an angle of approximately 45 degrees. This is done in order to avoid passing the needle completely through a thin right lobe, which might result in injury to the gallbladder or other structure beneath. To be relatively sure that the needle is in the liver, the patient is requested to inspire; if properly placed, the hub of the needle will swing cephalad. The obturator is withdrawn and suction applied by means of a 2 cc. syringe, in order to be sure that an excessively vascular area, a cyst or an abscess has not been entered.

The split biopsy needle is then inserted all the way into the needle in situ, which allows about 2 cm. of the split biopsy needle to extend beyond the end of the outer needle and to grasp the core of hepatic tissue. With the split biopsy needle held firmly in place, the outer needle is then rotated and advanced at the same time until it has reached the end of the inner needle. This will compress the core of tissues between the prongs of the split biopsy needle, and after one complete rotation the two needles are withdrawn simultaneously. The specimen is placed in a small quantity of 10 per cent formaldehyde for twenty-four hours and paraffin sections are made from it. The activities of the patient are not limited because of the procedure, but he is kept in the hospital at least twenty-four hours afterward for observation.

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27. The biopsies were performed at the Milwaukee County General Hospital, Wauwatosa, Wis., and the Veterans Administration Center, Wood, Wis.

The pathologic diagnoses made from the biopsy specimens of the liver are summarized in table 1. Classification of cases of portal cirrhosis into early, moderate and advanced types (fig. 1, 2, 3 and 4) was based on the degree and type of hepatic cell abnormality and the amount of fibrous tissue proliferation seen and is admittedly subjective in a small proportion of the cases. The diagnosis of cardiac cirrhosis (fig. 5) was made on specimens showing the changes of portal cirrhosis plus the dilated central vein. A history of long-standing cardiac disease was also given. The diagnosis of toxic cirrhosis was based also on observations in slides revealing decided increase in cellular infiltration in the periportal areas plus the changes of portal cirrhosis. A report of diagnosis of carcinoma (figs. 6, 7, 8 and 9) described the type of malignant condition as "adenocarcinoma" or "squamous cell carcinoma," but was seldom more specific. In several cases, an attempt was made to suggest the primary site of the malignant condition on the basis of the specimen alone, but this was not uniformly successful. Miscellaneous cases included 3 in which there was normal hepatic tissue and 4 in which there were nonspecific degenerative changes with pigmentation (fig. 10).

TABLE 1.—*Pathologic Diagnosis Made from Biopsy Specimens of the Liver*

Diagnosis	*No. of Cases*
Portal cirrhosis	
Early	14
Moderate	10
Advanced	23
Biliary cirrhosis	4
Toxic cirrhosis	3
Cardiac cirrhosis	3
Acute hepatitis	1
Carcinoma, metastatic (all types)	20
Brown degeneration	4
Hemochromatosis	4
Fatty metamorphosis	3
Amyloidosis	1
Miscellaneous	7

There were no deaths attributable to the biopsy of the liver in this series. Only three minor complications were observed. One was a small hematoma into the abdominal wall at the site of puncture and another a moderately severe hemorrhage noted during the procedure and followed by the development of a tender nodule in the area of puncture about one week after biopsy. This was interpreted as a hematoma either under Glisson's capsule or just outside the hepatic substance. Approximately 25 per cent of the patients complained of pain or vague abdominal discomfort during or shortly after the biopsy. The pain was seldom severe and occurred at the site of puncture or was referred to the chest or left flank. It did not last for more than an hour or two in any case, with the exception of four instances in which pain persisted for three to nine days. In none of these cases was an opportunity to search for underlying pathologic change afforded at autopsy.

The true value of needle biopsy of the liver in diagnosis is determined by a comparison of the results obtained from biopsy and the postmortem observations given in table 2. In addition, we have listed the clinical diagnoses, in order to emphasize the role of biopsy of the liver. Of 100 patients, 36 are known to have died, and autopsy was done on 19 (52.8 per cent) of these. Attempts at biopsy of the liver were unsuccessful in 3 of the autopsied patients. Concerning the remaining 16 cases, in case 5 failure occurred in that the metastatic lesions were missed when the biopsy needle passed within a few millimeters of two tumor nodules. The biopsy of the liver in case 7 confirmed the clinical impression and

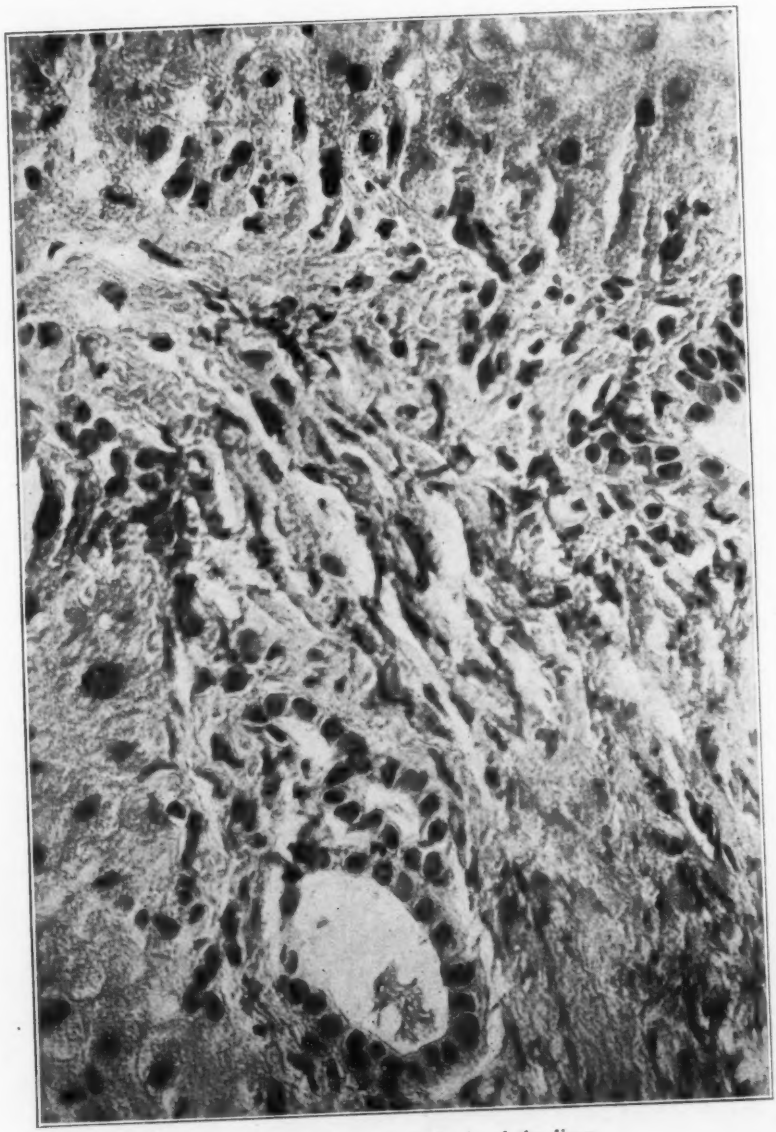

Fig. 1.—Early portal cirrhosis of the liver.

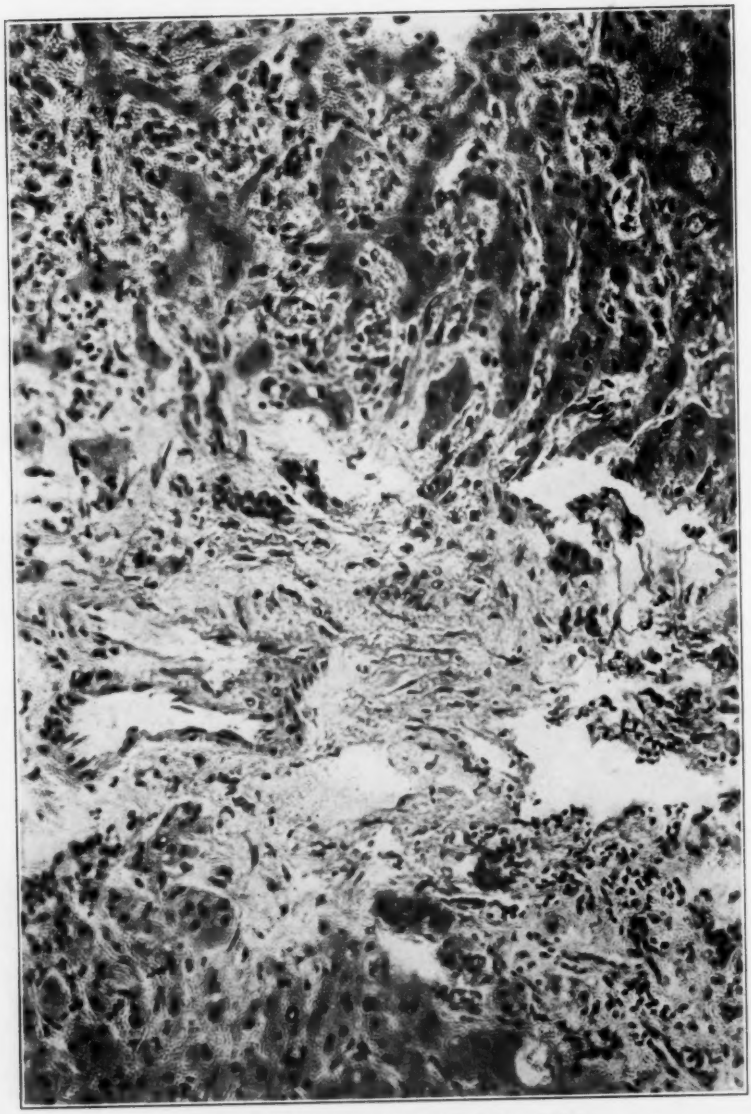

Fig. 2.—Moderate portal cirrhosis of the liver.

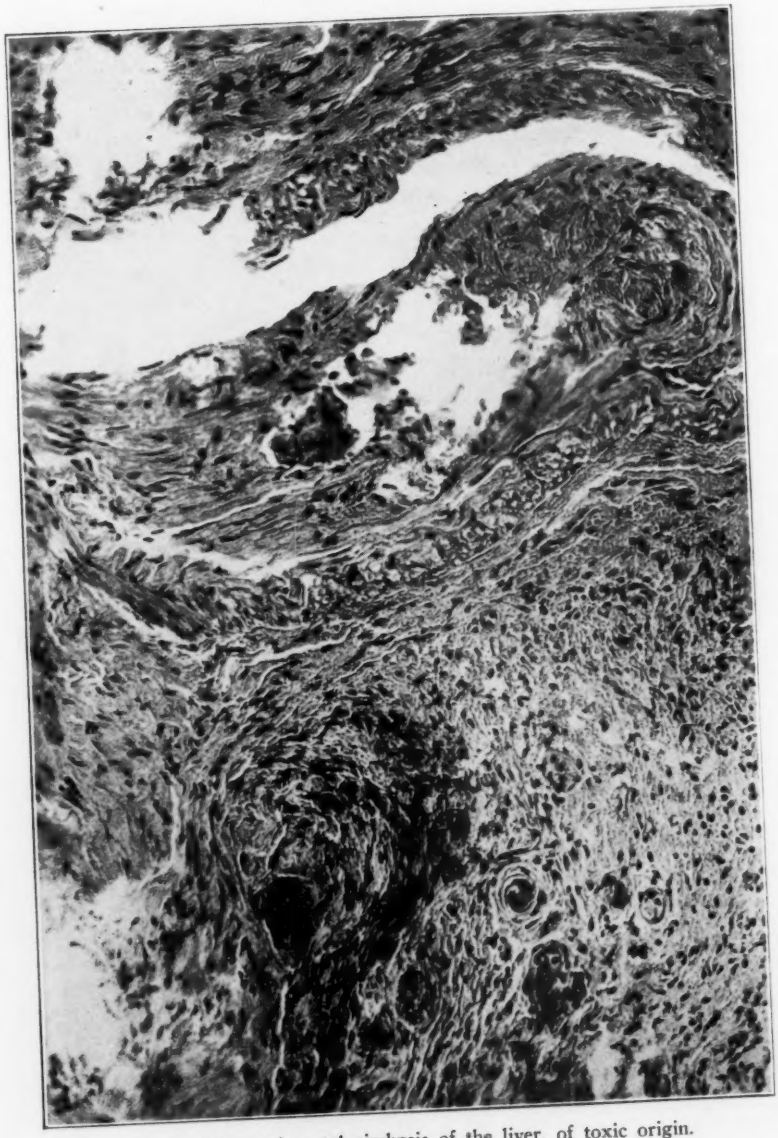

Fig. 3.—Advanced portal cirrhosis of the liver, of toxic origin.

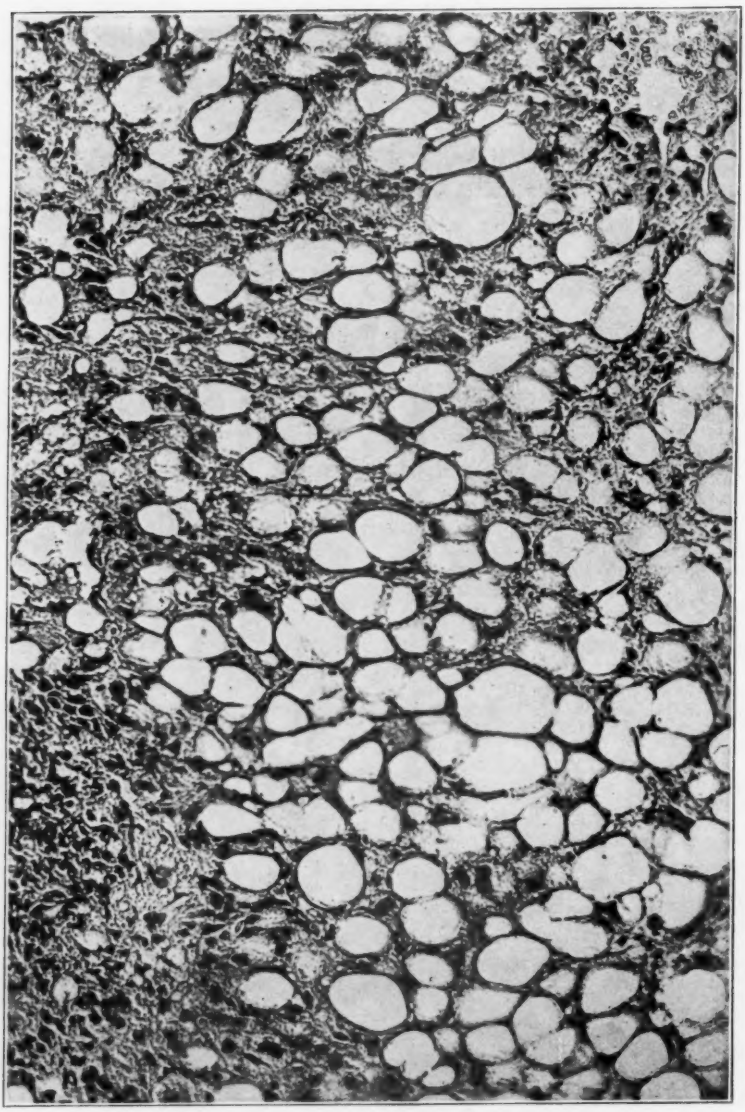

Fig. 4.—Portal cirrhosis of the liver, with decided fatty change.

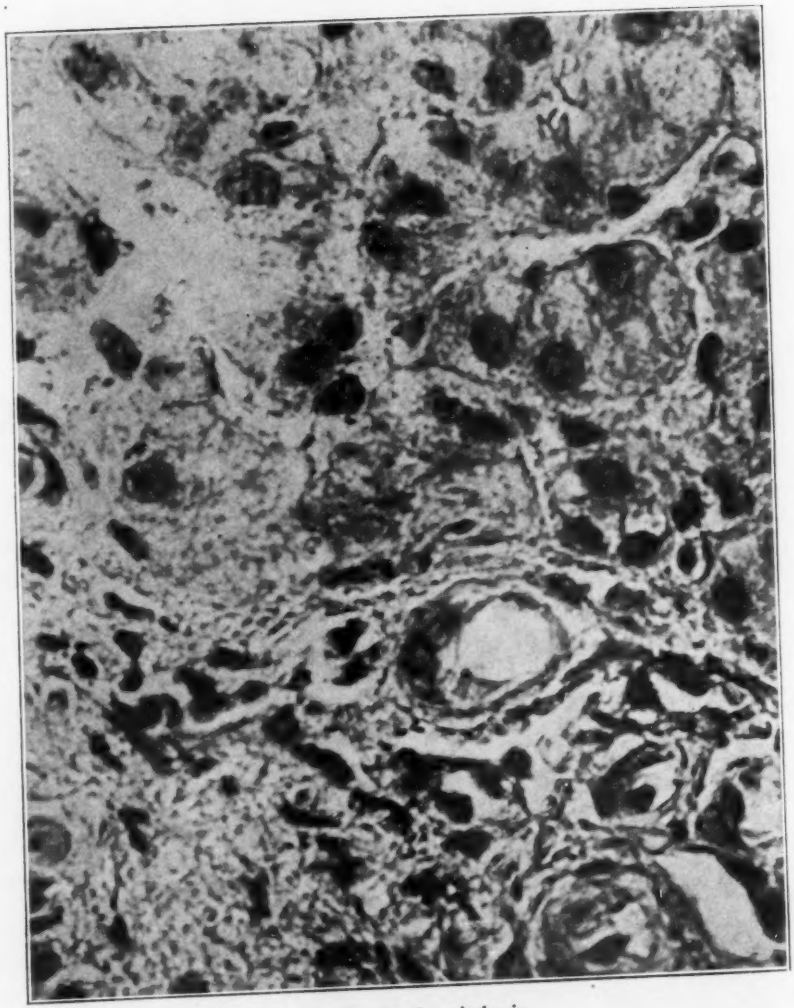

Fig. 5.—Cardiac cirrhosis.

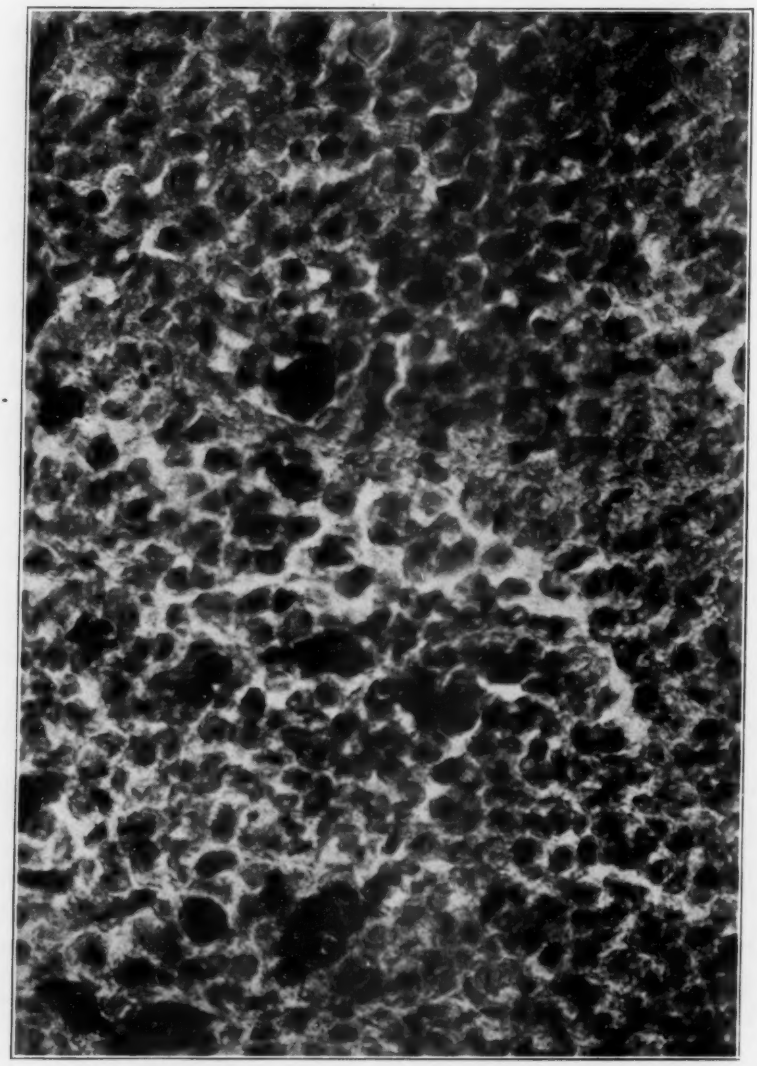

Fig. 6.—Metastatic melanosarcoma of the liver, from a patient with retrobulbar melanosarcoma.

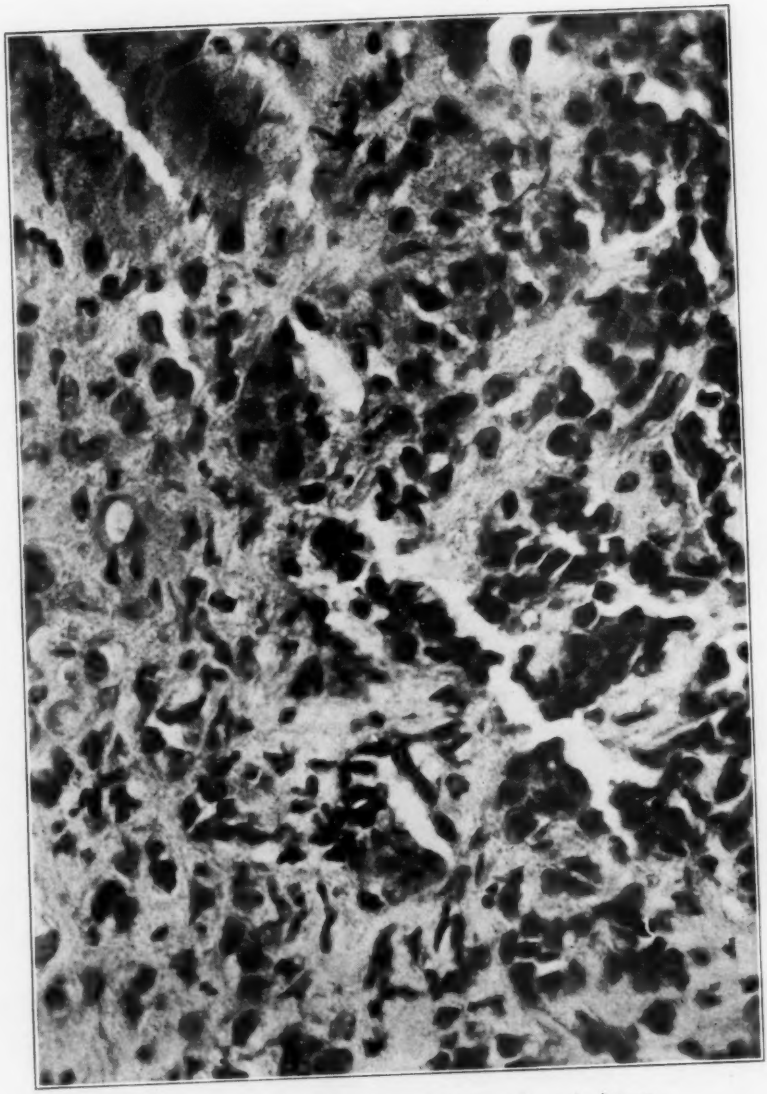

Fig. 7.—Metastatic carcinoma of the liver from the breast.

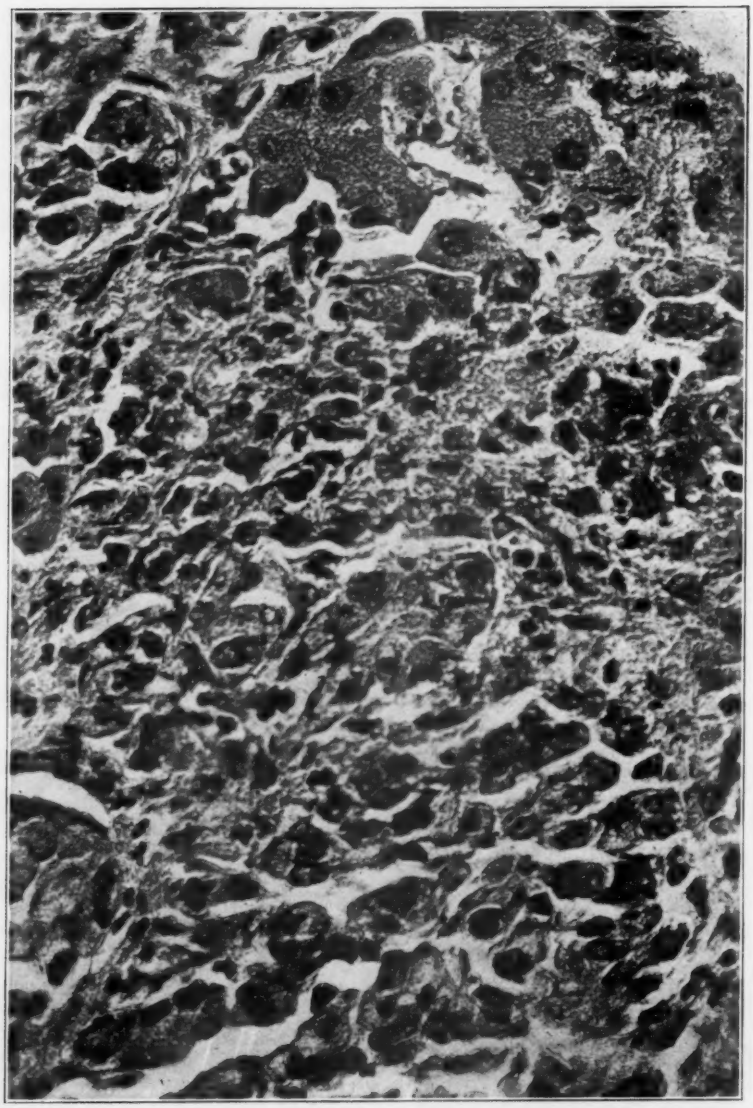

Fig. 8.—Metastatic carcinoma of the liver from the stomach.

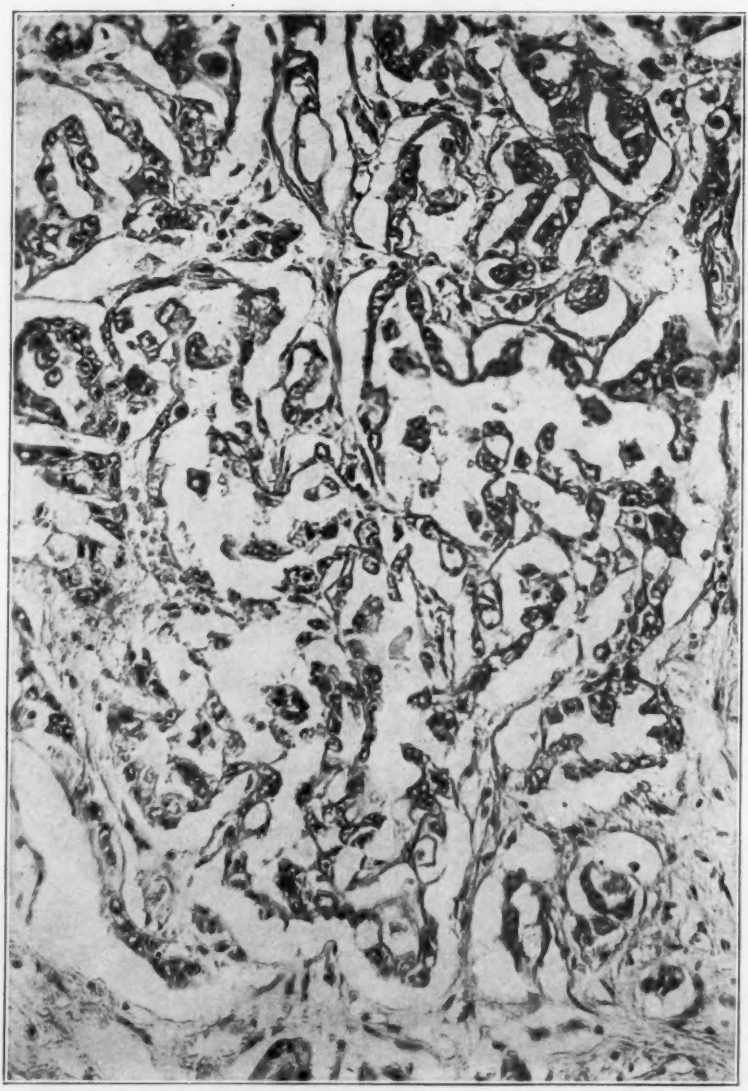

Fig. 9.—High grade metaplastic carcinoma of the liver, simulating squamous cell carcinoma, in a patient with carcinoma of the pancreas.

TABLE 2.—*Correlation of Clinical Diagnoses and Diagnoses from Biopsy of the Liver and Autopsy*

Case No.	Clinical Diagnosis	Diagnosis from Biopsy of the Liver	Diagnosis at Autopsy*
3	Extrahepatic obstructive jaundice, cause undetermined	Biliary type cirrhosis	Biliary cirrhosis due to carcinoma of the ampulla of Vater
5	Metastatic carcinoma of the liver, primary site undetermined	Normal hepatic tissue	Carcinoma of splenic flexure of the colon with metastasis to the liver
6	Portal cirrhosis	Portal cirrhosis (with fatty change)	Portal cirrhosis with chronic miliary tuberculosis of the lungs, intestines and peritoneum
7	Portal cirrhosis	Portal cirrhosis (early)	Portal cirrhosis and carcinoma of the gallbladder with local metastasis
8	Metastatic carcinoma of the liver, primary site undetermined	Metastatic adenocarcinoma	Carcinoma of the gallbladder with metastasis to the liver
9	Portal cirrhosis	Metastatic adenocarcinoma, suggested primary site is breast	Carcinoma of the breast with metastasis to the liver
10	Metastatic carcinoma of the liver, primary site undetermined	Metastatic adenocarcinoma	Primary carcinoma of the liver
11	Portal cirrhosis	Portal cirrhosis (advanced)	Portal cirrhosis (advanced)
12	Carcinoma of the colon with metastatic to the liver	Metastatic adenocarcinoma, suggested primary site is colon	Carcinoma of the descending colon with metastasis to the liver
13	Portal cirrhosis	Portal cirrhosis (advanced)	Portal cirrhosis (advanced)
15	Metastatic carcinoma of the liver	Metastatic adenocarcinoma, suggested primary site is colon	Carcinoma of prostate with metastasis to liver
16	Metastatic carcinoma of the liver	Metastatic adenocarcinoma	Carcinoma of stomach with metastasis to liver
17	Portal cirrhosis, multiple myeloma, pyelonephritis	Portal cirrhosis (advanced)	Portal cirrhosis (advanced), multiple myeloma, suppurative pyelonephritis
18	Metastatic carcinoma of the liver, primary site undetermined	Infiltrating carcinoma, apparently of squamous cell origin	Carcinoma of pancreas with metastasis to liver
19	Miliary infiltration—borh lungs (probably carcinoma)	Hemochromatosis	Hemochromatosis and bronchiectasis

*Attemps at biopsy of the liver were uncessful at autopsy in 3 cases.

demonstrated the pathologic changes in the liver, but it gave no clue to the primary cause of death. The biopsies in cases 1 and 51 (table 2) were done several months prior to death, at which time the primary cause was not suspected. There-

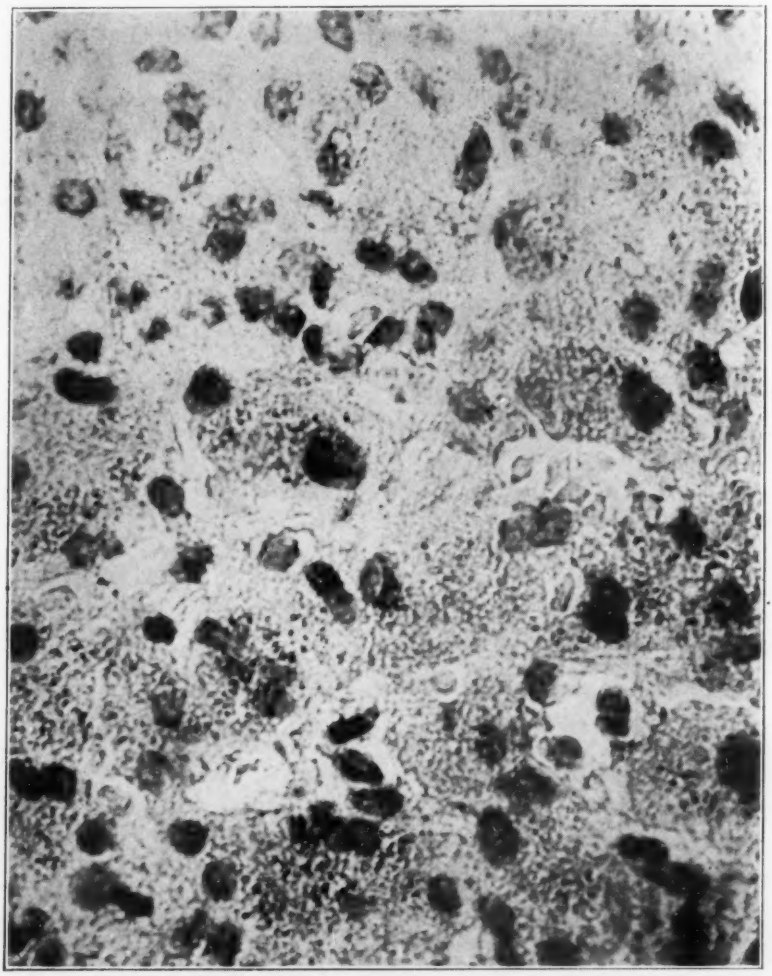

Fig. 10.—Brown degeneration of the liver of a patient with carcinoma of the colon.

fore, these two biopsies were considered to be diagnostic of the condition at that time. Analysis of these results reveals that in 14 cases (87.5 per cent) the diagnosis was either established or confirmed by biopsy of the liver.

REPORT OF CASES

CASE 1.—A. D., a 51 year old white man, was admitted to the hospital Dec. 30, 1946, complaining of cough, pain in the chest, chills, fever and hemoptysis of three days' duration. The patient was known to be diabetic for the past five years and had had one previous admission for control of his diabetes, during which a cutaneous test for hemochromatosis (Fishback) was reported as giving negative results. Physical examination revealed typical signs of pneumonia involving the lower lobe of the left lung. The liver was enlarged 6 cm. below the right costal margin and was smooth and nontender. The skin revealed generalized brownish dusky discoloration. A diagnosis of pneumonia was made and confirmed. The patient responded to treatment, and a biopsy of the liver was performed on

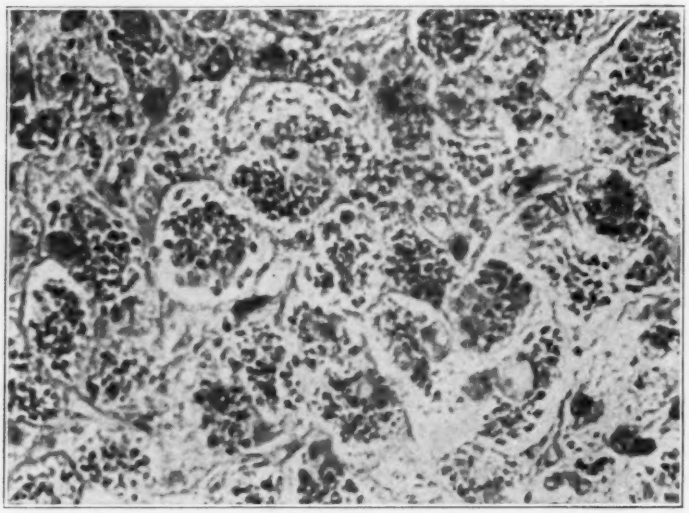

Fig. 11.—Hemosiderosis of the liver of a patient with hemochromatosis (iron stain).

December 12, because hemochromatosis was suspected. The report revealed the periportal connective tissue and the hepatic cells to be stippled with numerous pigment granules, which special stains showed to be iron, thus confirming the clinical diagnosis (fig. 11). A second Fishback test elicited negative results. The patient continued to improve and was discharged Jan. 27, 1947.

CASE 2.—W. S., a 53 year old white man, was admitted to the hospital March 21, 1946, complaining of fulness and tenderness in the tissues about the left eye. The present illness dated back to early in 1944, when the patient first noted swelling and pain in the left eye. He was admitted to the hospital in June 1944, at which time a diagnosis of melanosarcoma of the left eyeball was made and the eye enucleated. Physical examination revealed a well developed white man, with dis-

coloration and tenderness about the left orbital cavity. The liver extended down to the right iliac crest and below the navel in the midline. Roentgenograms of the chest revealed no metastatic lesions. Two biopsies of the liver were performed, the first, on June 25, 1946, showing normal hepatic tissue. The second biopsy, performed August 2, revealed melanosarcoma comprising the entire specimen (fig. 12). The patient's course was progressively downhill, and he died Jan. 7, 1947. Permission for autopsy was not obtained.

These cases illustrate instances in which biopsy of the liver proved to be the diagnostic measure. The intradermal cutaneous test for hemochromatosis as suggested by Fishback has not been a reliable one in our experience, a positive result being observed in only 1 of our 4 cases. In addition, a biopsy of the skin did not reveal hemochromatosis

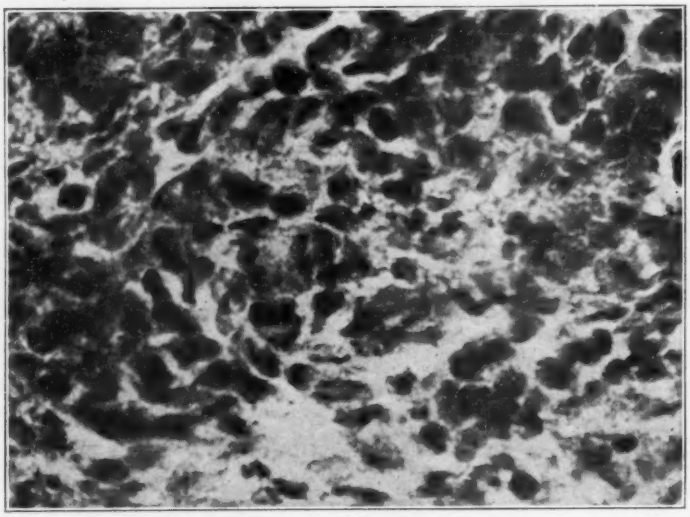

Fig. 12.—Melanosarcoma of the liver of a patient with retrobulbar melanosarcoma (special stain).

in 1 case. While the presence of metastatic lesions in the liver was suspected in the second case, this was not proved until after biopsy of the liver. Metastatic lesions elsewhere could not be demonstrated by the usual means.

CASE 3.—A. H., a 47 year old white man, was admitted to the hospital complaining of weakness and painless intermittent jaundice of nine months' duration. His stools had been acholic at times and his urine dark. He had lost 20 pounds (about 9 Kg.) in weight since the onset of his illness. Previous gastrointestinal roentgenograms revealed no abnormalities. Physical examination revealed the patient to be extremely jaundiced. The liver was palpable 10 cm. below the right costal margin and was nodular and tender. Gastrointestinal roentgenograms while the patient was in the hospital again failed to reveal abnormalities. Examination

Fig. 13.—Decided biliary cirrhosis of the liver.

of the blood revealed moderate anemia, and results of urinalysis were positive for bile and negative for urobilinogen on many occasions. The icterus index varied from 65.0 to 152.0, with a direct immediate van den Bergh reaction. Biopsy of the liver was performed on Sept. 28, 1946, and revealed biliary type hepatic cirrhosis (fig. 13). After several transfusions, a laparotomy was performed on October 25, which revealed obstruction of the distal common duct, with biliary cirrhosis. The cause of this obstruction could not be determined, and a cholecystogastrostomy was performed. A biopsy of the pancreas was made, and the patient later had abdominal hemorrhage and fibrinous peritonitis and died November 2. Autopsy revealed the cause of the obstruction to be an extremely small carcinoma of the ampulla of Vater.

CASE 4.—W. G.. a 52 year old white man, was admitted to the hospital Feb. 26, 1946, because of ankylosis of the jaw. The patient gave a history of joint

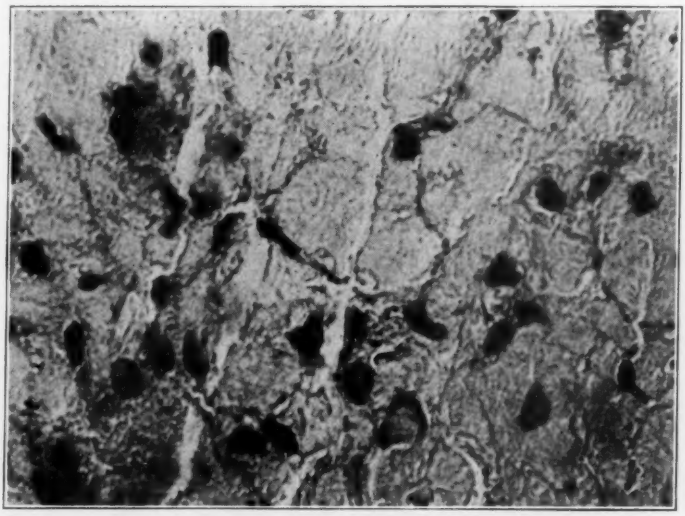

Fig. 14.—Amyloidosis of the liver, with almost complete destruction of architecture (special stain).

pain and later ankylosis, dating back twenty-nine years. Physical examination revealed an emaciated man with the typical signs of rheumatoid arthritis involving the shoulders, hands and knees bilaterally. In addition, there was a so-called "poker spine" and ankylosis of both temperomandibular joints. The liver was palpable at the right iliac crest and was smooth and nontender. Because amyloidosis of the liver was suspected, a biopsy was performed October 19. The liver revealed advanced amyloid degeneration (fig. 14). The congo red test resulted in the retention of less than 20 per cent of the dye in the blood in one hour.

In case 3, the biopsy of the liver differentiated jaundice due to obstruction and that due to parenchymatous hepatic disease or cholangiolitis, thereby justifying laparotomy. This particular biopsy cannot be called a diagnostic one in the strict sense of the term, since

the underlying cause of the jaundice remained obscure until autopsy, but it was in agreement with the clinical picture. In case 4, the suspicion of amyloidosis of the liver was confirmed.

CASE 5.—A. B., a 54 year old white man, was admitted to the hospital complaining of sharp pains around the umbilicus, anorexia, watery diarrhea and a loss of 15 pounds (about 7 Kg.) in weight, of five weeks' duration. Physical examination showed an emaciated patient who appeared chronically ill. The abdomen was distended and the liver greatly enlarged and nodular, extending down to the right iliac crest and to the level of the navel in the midline. Examination of the blood revealed moderate anemia, which became progressively severer. Roentgenograms of the gastrointestinal tract, kidneys, ureter and bladder revealed evidence of a mass in the abdomen, but none of them localized the lesion to any one organ. Biopsy of the liver was performed on June 26, 1946, and

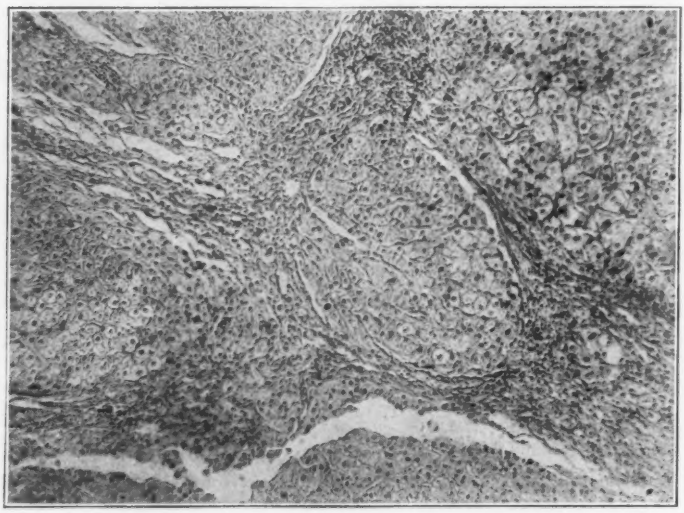

Fig. 15.—Advanced portal cirrhosis of the liver (Van Gieson stain).

showed normal hepatic tissue. The patient became progressively weaker and died July 24. Autopsy revealed a carcinoma of the splenic flexure of the colon, with metastasis to all the abdominal organs, especially the liver. It was noted that the biopsy needle had been inserted into the liver and had passed within several millimeters of two metastatic tumor nodules.

CASE 6.—M. P., a 45 year old Mexican woman, was admitted to the hospital April 19, 1946, with the complaint of weakness, anorexia, vomiting and abdominal pain and distention of one month's duration. The patient had noted jaundice for four days prior to admission. There was a history of chronic alcoholism of long duration. Physical examination revealed an emaciated patient in some distress. The liver was enlarged 10 cm. below the right costal margin and was smooth and moderately tender. There was slight icterus of the scleras and mucous membranes. Numerous procedures, including roentgenograms of the chest and gastro-

intestinal tract and examination of abdominal fluid and sputum failed to reveal any specific diagnosis. A biopsy of the liver, performed on September 14, revealed advanced portal cirrhosis (fig. 15). The patient pursued a downhill course and died September 23. Autopsy revealed chronic miliary tuberculosis, involving the lungs, intestines and peritoneum, with portal cirrhosis and bronchopneumonia.

The aforementioned cases illustrate instances in which the biopsy of the liver was not in agreement with the clinical picture. Case 5 is an example of one of the limitations inherent in the procedure. In case 6, the report of biopsy might be considered misleading, since the clinical picture was not clearcut and the presence of portal cirrhosis, diagnosed at biopsy, provided definite evidence of a condition which could satisfactorily explain it. Thus, the diagnosis of tuberculosis was given less prominence than it would have been had normal hepatic tissue been obtained.

COMMENT

From a clinical standpoint, biopsies may be classified into those which are helpful in determining the diagnosis and those which are not. Included in the helpful group are those biopsies which are diagnostic and those which are in agreement with the clinical picture, but which do not reveal the underlying pathologic condition. Biopsies considered not to be helpful are those which were not in agreement with the clinical picture and the failures. The classification is, of course, subjective to a certain extent. On this basis, eighty-three biopsies (75 per cent) were considered helpful and twenty-eight biopsies (25 per cent) not helpful. If the 14 cases in which no tissue was obtained for study are eliminated, 86 per cent of the biopsies were observed to aid in the diagnosis. These observations compare favorably with those of other writers.[28]

The specimen of liver obtained in our cases consisted of a core of tissue from 10 to 20 mm. in length and approximately 2 mm in width. From the pathologic standpoint, these specimens offer the advantages of minimum autolysis, which permits a cytologic study generally superior to that afforded at autopsy. The specimens fixed in alcohol for the purpose of studies of glycogen are admittedly more satisfactory than specimens obtained at autopsy. In addition, biopsy may be performed at intervals, thus enabling one to follow the progress of pathologic changes and to evaluate the effects of treatment.

The principal disadvantage of the specimen is its size, which offers a relatively small area for visualization. Thus, a completely objective diagnosis is sometimes not possible. Compression and shredding of the specimen during the biopsy procedure causes distortion of the tissues in some instances. Comparison of the specimens obtained at autopsy and

28. Hoffbauer, Evans and Watson.[20] Davis, Scott and Lund.[24]

those obtained by biopsy revealed that in a majority of cases the biopsy specimen was a good sample of the changes in the entire liver. This has been commented on by Sherlock.[14]

Although not within the scope of this paper, it is interesting to note the correlation of tests of hepatic function with the pathologic changes revealed by biopsy. Two or more tests of hepatic function were performed on 74 patients in this series. After reviewing these determinations and comparing them with the pathologic observations in the biopsy specimen, we were unable to correlate the results. Cases in which the disease was classified as early portal cirrhosis by means of the biopsy sometimes revealed significant impairment in one or several tests of hepatic function, while in many instances the cases of far advanced disease revealed little impairment. This is in agreement with the report of Hoffbauer, Evans and Watson.[23] The lack of correlation was evident also in some of the cases of metastatic carcinoma of the liver. In a review of macrocytosis associated with disease of the liver, Weintrobe[29] stated that this observation was present in 32.6 per cent of 132 cases of varied forms of hepatic disease, and he pointed out that this is noted only in cases of hepatic disease of long duration and of wide extent. Hematocrit studies were done in 29 of our cases, and macrocytosis (mean cell volume more than 95.0 cubic microns) was observed in 18 cases (62 per cent). There was no anemia in 17.2 per cent, macrocytic anemia in 55.3 per cent, normocytic anemia in 17.2 per cent and microcytic anemia in 10.3 per cent. Chronic loss of blood was a factor in most of the last-mentioned group.

We believe that needle biopsy of the liver has established itself as a valuable aid in the diagnosis of diseases of the liver. As previously stated, the clinical picture is often confusing, and in the majority of our cases the biopsy confirmed clinical impressions or revealed the presence of an unsuspected lesion. In addition to the use of biopsy of the liver in any case of hepatomegaly of undetermined origin, the fact that several biopsies may be performed on patients over a period of time permits an evaluation of treatment in chronic hepatic diseases, such as cirrhosis. The procedure also affords an opportunity for vital studies of living hepatic tissue, which may aid materially in elucidating the normal physiologic function of the liver or alteration of its metabolic processes and, as has been reported frequently since 1939, an investigation of hepatic changes in epidemic hepatitis, toxic hepatitis and spirochetal jaundice (Weil's disease).

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29. Weintrobe, M. W.: Clinical Hematology, Philadelphia, Lea & Febiger, 1946, p. 399.

Limitations of the procedure are those associated with random sampling which may miss a focal lesion, as illustrated in 1 case (case 5). Biopsies performed in 2 cases of polycystic disease of the liver, as proved by laparotomy, failed to yield any tissue. Thus, hepatic disease of a diffuse nature is most readily detectable.

The hazards associated with the intercostal approach in biopsy of the liver are apparent on reviewing the papers in which this method was used. The greatest danger is hemorrhage, as pointed out by Raby,[30] in 1944, in a review of 7 previously reported cases of fatal hemorrhage, to which he added 1 case of his own. This was also commented on by Toullec and Huard.[31] The bleeding in these cases was attributed to the fact that the needle is held firmly between the ribs and the liver is torn as it moves coincident with respiration. In addition, the pleural sac is exposed to the danger of infection in this approach. The procedure requires the complete cooperation of the patient, who must hold his breath in expiration during the entire time the needle is inserted, the syringe attached and the needle advanced into the liver and withdrawn. Because of these potential dangers, we join other writers[32] in recommending that biopsy of the liver be performed from a subcostal approach only and that the liver be palpated at least 4 cm. below the thoracic cage.

Other complications include the introduction of infection into the peritoneal cavity or the abdominal wall and perforation of, or injury to, nearby viscera, such as the intestines, gallbladder, kidneys, adrenals or pancreas. Baron[17] reported the recovery of a piece of colonic mucosa in 1 case, without untoward results. Davis, Scott and Lund[24] reported puncture of the gallbladder by transfixing the right lobe of the liver in 1 case and obtained duodenal mucosa in another, without complications. Further precautions include determination of the bleeding, clotting and prothrombin times, especially in jaundiced patients. The prothrombin time (Quick's method) was performed in 47 of our cases. Vitamin K preparations were administered when indicated, and tests of the prothrombin time were repeated prior to biopsy in these instances. Biopsies of the liver should be avoided in the region of the gallbladder and are precluded in the presence of severe ascites and abdominal distention secondary to ileus.

If the aforementioned precautions are observed, needle biopsy of the liver carries with it relatively little risk and yields valuable information in the majority of cases.

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30. Raby, K.: Complications and Dangers of Liver Biopsy, Nord. med. (Hospitalstid.) **24**:2161-2164 (Dec. 8) 1944.

31. Toullec, F., and Huard, P.: La ponction exploratrice du foie (dangers, indications, contre-indications), Monde méd., Paris **45**:990-999 (Nov. 15) 1935.

32. Baron.[17] Tripoli and Fader.[21] Hoffbauer.[22] Davis, Scott and Lund.[24]

SUMMARY

One hundred and eleven biopsies of the liver in 100 patients, with the Vim-Silverman needle, are reported. Of these, ninety-seven biopsies (87.4 per cent) were successful and fourteen biopsies (12.6 per cent) were failures. There were no fatalities or serious complications. Of the successful biopsies, eighty-three (86 per cent) were considered to be helpful in the diagnosis.

The indications and complications of needle biopsy of the liver have been pointed out and commented on.

We recommend that biopsy be performed only when the liver is easily palpable. The intercostal approach is not advocated, and biopsies should be avoided in the region of the gallbladder and in cases of ascites and abdominal distention due to ileus. In addition, bleeding, clotting and prothrombin times should be normal, and facilities for blood transfusion should be readily available.

NOTE.—Since this paper was submitted for publication we have performed two hundred and fifty additional biopsies of the liver, using the same technic and criterion. There have been no fatalities in our series to date, and only 4 patients showed clinical evidence of hemorrhage, all of whom responded to conservative therapy.

870 West Wisconsin Avenue.

PLASMA LIPIDS IN PRIMARY (XANTHOMATOSIS) AND SECONDARY HYPERCHOLESTEREMIA

I. The Effect of Lipotropic Substances

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HYPERCHOLESTEREMIA is a common observation in some well recognized metabolic disorders. The elevated level of cholesterol in the serum may represent a primary defect in the metabolism of this sterol (xanthomatosis)[1] or may signify a derangement in lipid metabolism secondary to some underlying metabolic disturbance, such as diabetes mellitus, hypothyroidism and nephrosis. The present study embraces both types of hypercholesteremia. The first part of the investigation is concerned with the effect of several lipotropic substances on the plasma lipids and the second, which will be reported later, with diets low in cholesterol values.

MATERIAL AND METHODS

Thirteen patients were studied. The disease in 9 of these was classified as primary (essential) xanthomatosis with hypercholesteremia[2] and in 4 as secondary hypercholesteremia due to various metabolic disorders. The clinical data on these patients are detailed in table I.

The following lipotropic materials[3] were used (oral route): (*a*) vitamin E, synthetic d,l-alpha-tocopherol acetate or mixed natural tocopherols, in 7 patients with primary (essential) xanthomatosis, for twelve to fifty weeks (table 2), (*b*)

Aided by a grant from the New York Diabetes Association.

From the Division of Cardiology and the Medical Research Laboratory, Department of Medicine, New York Post-Graduate Medical School and Hospital, New York.

1. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, Ann. Int. Med. **11**:1662-1746 (March) 1938. Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, New York, Oxford University Press, 1940.

2. Dr. H. H. Ritter referred to us the patients in cases 2 and 3.

3. Hoffman-LaRoche, Inc., Nutley, N. J., supplied the d,l-alpha-tocopherol; Eli Lilly and Company, Indianapolis, supplied the mixed natural tocopherols; the American Lecithin Co., Inc., Elmhurst, N. Y., supplied the oil-free and crude lecithin; Dr. Lester R. Dragstedt, Chicago, supplied the lipocaic, and Sharpe & Dohme, Inc., Philadelphia, supplied the pancreatic extract.

oil-free or crude lecithin in, 4 patients with primary (essential) xanthomatosis, for eight to fifteen weeks (table 3), (*c*) lipocaic[4] or pancreatic extract with lipocaic-like properties, in 1 patient with primary (essential) xanthomatosis, for twenty-four and fourteen weeks, respectively (table 4), and (*d*) vitamin E, d,1-alpha-tocopherol acetate or mixed natural tocopherols, in 4 patients with secondary

TABLE 1.—*Clinical Data for 9 Patients with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type and 4 Patients with Secondary Hypercholesteremia Herein Investigated*

Case No.	Age (Yr.)	Sex	Relationship	Diagnosis	Comment
1	35	M	.....	Xanthoma tuberosum; xanthomatous tendon sheath tumor; probable xanthomas of coronary arteries	Acute posterior myocardial infarct at age of 33
2	35	M	Brother of patient in case 3	Xanthomatous tendon sheath tumor	.....
3	34	F	Sister of patient in case 2	Xanthomatous tendon sheath tumor	
4	18	F	.....	Arcus juvenilis (xanthomatous involvement of cornea); xanthoma tuberosum; probable xanthomatous involvement of endocardium; probable xanthomas of coronary arteries	Harsh high pitched precordial murmur; T waves in leads II and III of the electrocardiogram were sharply and deeply inverted; cardiac failure developed in December 1944 and 3 weeks later the patient died suddenly while defecating
5	11	M	Brother of patient in case 6	Arcus juvenilis (xanthomatous involvement of cornea); xanthoma tuberosum; probable xanthomatous involvement of endocardium	Harsh high pitched systolic murmur, loudest at aortic area; harsh, low pitched systolic murmur, loudest at mitral area
6	14	M	Brother of patient in case 5	Xanthomatous involvement of tendon sheaths	.....
7	49	F	.....	Xanthoma tuberosum	.....
8	44	F	.....	Xanthoma tuberosum	.....
9	35	M	.....	Xanthoma tuberosum	.....
12	49	M	.....	Diabetes mellitus	Mild degree; good control with little or no insulin; glycosuria and hyperglycemia rare
13	72	F	.....	Cholecystitis and cholelithiasis	.....
14	39	M	.....	Diabetes mellitus; chronic nephritis	Possibility of intercapillary glomerulosclerosis
15	45	M	.....	Diabetes mellitus	Possibility of primary (essential) xanthomatosis, because of associated splenomegaly and leukopenia, but this diagnosis not definitely established

hypercholesteremia due to various metabolic disturbances (e.g., diabetes mellitus, cholecystitis and cholelithiasis, and chronic nephritis), for six to twelve weeks (table 5).

Prior to the administration of the lipotropic substances, two or three fasting serum cholesterol determinations were made at intervals of one or two weeks

4. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**:175-181 (Sept.) 1936.

except in case 3 (table 2) and cases 12, 13, 14 and 15 (table 5), in which only one control observation was made. In several studies (tables 2 and 5) the total lipids and fatty acids in the plasma were also estimated.[5] In most instances, the plasma lipids or serum cholesterol determinations were made at intervals of two weeks during the experimental period.

The total plasma lipids were estimated by the procedure of Bloor.[6] Plasma or serum cholesterol was determined by the method of Sackett.[7] Total fatty acids were calculated by the difference between total lipids and cholesterol values.[6b] The range for these lipid components in normal subjects by these procedures is as follows: cholesterol 160 to 230 mg. per hundred cubic centimeters, total lipids 500 to 700 mg. per hundred cubic centimeters and total fatty acids 200 to 420 mg. per hundred cubic centimeters.

RESULTS

Table 2 shows that the ingestion of d,l-alpha-tocopherol acetate or mixed natural tocopherols over a period of twelve to fifty weeks by 7 patients with primary (essential) xanthomatosis and hypercholesteremia failed to decrease the level of the blood lipids. The decrease in the serum cholesterol in the patient (case 3) with xanthomatous tendon sheath tumor may be ascribed to the diet low in cholesterol which was simultaneously prescribed, since discontinuation of the diet on the thirty-first week of observation was promptly followed by an increase in the serum cholesterol even though the administration of tocopherols was uninterrupted.

Table 3 reveals that the ingestion of oil-free or crude lecithin, in appreciable doses over a period of eight to fifteen weeks by 4 patients with primary (essential) xanthomatosis, likewise failed to decrease the level of the serum cholesterol.

In 1 patient with arcus juvenilis, xanthoma tuberosum and probable xanthomatous involvement of the endocardium (case 5), the oral administration of 6 Gm. of lipocaic per day for twenty-four weeks followed by administration of 6 Gm. of pancreatic extract with lipocaic-like properties for an additional fourteen weeks did not diminish the serum cholesterol (table 4).

Table 5 shows that the oral administration of d,l-alpha-tocopherol acetate or mixed natural tocopherols, over a period of six to twelve

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5. Miss Frances Lauber gave technical assistance.

6. (*a*) Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: The Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**:191-205 (May) 1922. (*b*) Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. ibid. **77**:53-73 (April) 1928.

7. Sackett, G. E.: Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum, J. Biol. Chem. **64**:203-205 (May) 1925.

TABLE 2.—*Effect of Vitamin E on the Plasma Lipids of 7 Patients with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type*

Case No.	Blood Lipids (Mg./100 Cc.) and Medication	Weeks of Study 0	2	4	6	8	10	12	14	Comment
1	Total lipids	1,780	1,874	1,972	1,685	1,645	1,530	1,822	--	Serum cholesterol determinations continued for 47 weeks (8 additional analyses); values ranged from 330 to 530 mg. with an average of 450 mg. per 100 cc.; medication consisted of 300 mg. of mixed natural tocopherols per day except for the twentieth to twenty-fourth week, when no medication was given
	Fatty acids	1,370	1,424	1,554	1,299	1,232	1,232	1,344	--	
	Cholesterol	410	450	418	386	413	417	478	390	
	Tocopherols per day (mg.)	None	None	None	300*	300*	300†	300†	300†	
2	Cholesterol	375	355	445	--	--	--	290	395	Serum cholesterol determinations continued for 22 weeks (2 additional analyses); values were 445 and 375 mg., with an average of 410 mg. per 100 cc.; medication consisted of 300 mg. of mixed natural tocopherol per day
	Tocopherols per day (mg.)	None	None	None	300†	300†	300†	300†	300†	
3	Total lipids	1,116	800	1,093	--	--	--	--	--	Serum cholesterol determinations continued for 50 weeks (4 additional analyses); low cholesterol diet and mixed tocopherols were continued until the twenty-fourth week, when the serum cholesterol was 300 mg. per 100 cc.; thereafter a low cholesterol diet alone was prescribed and the serum cholesterol at the thirty-first week was 195 mg. per 100 cc.; patient voluntarily discontinued the diet from the thirty-first week on; serum cholesterol at the thirty-fifth and fiftieth week of observation was 315 and 335mg. per 100 cc., respectively
	Fatty acids	676	397	665	--	--	--	--	--	
	Cholesterol	440	403	428	--	355	--	295	--	
	Tocopherols per day (mg.)	None	300†‡	300†‡	300†‡	300†‡	300†‡	300†‡		
5	Total lipids	1,709	1,808	1,770	--	1,811	--	1,587	1,674	----------
	Fatty acids	1,006	1,183	1,157	--	1,186	--	993	1,044	
	Cholesterol	703	625	613	--	625	--	594	630	
	Tocopherols per day (mg.)	None	None	None	75*	75*	75*	75*	300†	
6	Total lipids	1,358	1,525	1,774	--	1,381	1,455	1,352	--	
	Fatty acids	810	895	1,174	--	834	912	764	--	
	Cholesterol	548	630	600	--	547	543	588	--	
	Tocopherols per day (mg.)	None	None	None	75*	75*	300†	300†	--	
7	Total lipids	2,297	2,176	2,877	2,943	2,448	2,552	1,860	--	Serum cholesterol determinations continued for 40 weeks (5 additional analyses); values ranged from 420 to 895 mg. per 100 cc.; with an average of 686 mg.; medication consisted of 300 mg. of mixed natural tocopherols per day except for the eighteenth to twenty-second week, when no medication was given
	Fatty acids	1,737	1,576	2,230	2,273	1,788	1,899	1,225	--	
	Cholesterol	560	600	647	670	660	653	635	--	
	Tocopherols per day (mg.)	None	None	None	300*	300*	300†	300†	--	
8	Total lipids	1,860	1,756	1,795	1,729	1,823	1,600	--	--	Serum cholesterol determinations continued for 22 weeks (2 additional analyses); values were 660 and 740 mg., with an average of 700 mg. per 100 cc.; no medication given
	Fatty acids	1,245	1,256	1,270	1,229	1,323	1,150	--	--	
	Cholesterol	615	500	525	500	500	450	475	543	
	Tocopherols per day (mg.)	None	None	None	150*	300*	300*	300†	300†	

*In the form of d,l – alpha – tocopherol acetate.
†Mixed natural tocopherols.
‡With a diet low in cholesterol content.

weeks, to 4 patients with secondary hypercholesteremia due to recognizable metabolic defects (diabetes mellitus, cholecystitis and cholelithias, chronic nephritis) failed to decrease the level of the plasma

TABLE 3.—*Effect of Lecithin on the Serum Cholesterol of Patients with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type*

Case No.	Serum Cholesterol (Mg./100 Cc.) and Medication	Weeks of Study												
		0	2	3	4	5	6	7	8	9	10	12	13	15
1	Serum cholesterol	410 450 418	--	335	--	290	--	440	--	335	--	--	--	--
	Lecithin per day (Gm.)	None	24*	24*	24*	24*	24*	24*	24*	24*	--	--	--	--
2	Serum cholesterol	375 355 445	--	--	355	--	375	--	395	--	--	--	--	--
	Lecithin per day (Gm.)	None	24*	24*	24*	12*	12*	12*	12*	--	--	--	--	--
4	Serum cholesterol	525 530	--	--	535	--	485	--	610	--	565	--	490	475
	Lecithin per day (Gm.)	None	18†	18†	18†	18†	18†	27‡	27‡	27‡	27‡	54§	54§	54§
9	Serum cholesterol	375 420 350	420	--	460	--	355	--	360	--	510	340	--	--
	Lecithin per day (Gm.)	None	24♦	24♦	24♦	36¶	36¶	36¶	36¶	36¶	36¶	18†	--	--

*Oil-free lecithin (granulated phosphatides).
†Six "lexo wafers." (Each wafer contains 3 Gm. of soybean lecithin, 1,000 U. S. P. units of vitamin A, 100 U. S. P. units of vitamin D, 165 U. S. P. units of thiamine and 81 mg. of phosphorus.)
‡Nine "lexo wafers."
§Eighteen "lexo wafers."
♦Eight "lexo wafers."
¶Twelve "lexo wafers."

TABLE 4.—*The Effect of Pancreatic Extracts on the Serum Cholesterol of a Patient with Primary (Essential) Xanthomatosis of the Hypercholesteremic Type (Case 5)*

Weeks	Lipocaic per Day (Gm.)	Pancreatic Extract per Day (Gm.)	Serum Cholesterol (Mg./100 Cc.)
0	--------	--------	703 625 613
5	6	--------	700
8	6	--------	580
15	6*	--------	490
21	6†	--------	660
24	6	--------	680
28	--------	6	535
32	--------	6	500
35	--------	6	510
38	--------	6	810

*The patient received no lipocaic for fourteen days during this period, because of disease of the respiratory tract.
†The patient took no lipocaic for eight days before determination of serum cholesterol.

cholesterol. In 2 patients (cases 12 and 13) there was a suggestive fall in the total plasma lipids and fatty acids, but the plasma cholesterol remained unchanged.

COMMENT

The lipotropic effect of vitamin E was first described by Dam and Kelman,[8] who demonstrated a reduction in the fasting plasma lipids of vitamin E-deficient chicks after the administration of vitamin E. Subsequent studies by Dam[9] and by Bruger[10] showed that the atherosclerosis produced in rabbits fed a diet high in cholesterol was not diminished by

TABLE 5.—*Effect of Vitamin E on the Plasma Lipids of Patients with Hypercholesteremia Due to Metabolic Disturbance Other Than Xanthomatosis*

Case No.	Blood Lipids (Mg./100 Cc.) and Medication	0	Weeks of Study					
			2	4	6	8	10	12
12	Total lipids	1,770	--	1,478	1,536	1,490	1,265	1,029
	Fatty acids	1,192	--	970	1,020	995	797	506
	Cholesterol	578	--	508	516	495	468	523
	Tocopherols per day (Mg.)	None	150*	150*	300*	300*	300[0]	300[0]
13	Total lipids	1,044	--	--	920	--	--	--
	Fatty acids	714	--	--	592	--	--	--
	Cholesterol	330	--	--	328	--	--	--
	Tocopherols per day (Mg.)	None	150*	150*	150*	--	--	--
14	Total lipids	828	--	918	--	1,047	--	--
	Fatty acids	502	--	630	--	704	--	--
	Cholesterol	326	--	288	--	343	--	--
	Tocopherols per day (Mg.)	None	150*	150*	150*	150*	--	--
15	Total lipids	4,412	--	4,368	--	4,542	--	4,791
	Fatty acids	4,027	--	3,980	--	4,187	--	4,411
	Cholesterol	385	--	388	--	355	--	380
	Tocopherols per day (Mg.)	None	150*	150*	150*	150*	300[0]	300[0]

*Synthetic d, l-alpha-tocopherol acetate.
[0]Mixed natural tocopherols.

simultaneous administration of d,l-alpha-tocopherol acetate. On the contrary, Bruger, using dosages of vitamin E almost four times the dosage used by Dam demonstrated an appreciable increase in the amount of cholesterol deposited in the aorta. In the present study, no reduction in serum lipids was obtained following the prolonged administration of moderate or large doses of d,l-alpha-tocopherol acetate or mixed natural tocopherols to patients with primary (essential) xanthomatosis and hypercholesteremia. In 4 patients with secondary hypercholesteremia, vitamin E likewise failed to influence the level of the plasma cholesterol, but it apparently caused a reduction in the total plasma lipids and fatty acid in 2 of these patients.

8. Dam, H., and Kelman, E. M.: The Effect of Vitamin E on the Blood Plasma Lipids of the Chick, Science **96**:430 (Nov. 6) 1942.

9. Dam, H.: Ineffectiveness of Vitamin E in Preventing Cholesterol Deposition in the Aorta, J. Nutrition **28**:289-295 (Oct.) 1944.

10. Bruger, M.: Experimental Atherosclerosis: VII. Effect of Vitamin E, Proc. Soc. Exper. Biol. & Med. **59**:56-57 (May) 1945.

Soybean lecithin contains choline, inositol and cephalin in approximately equal proportions. In the wafer form, it contains soybean oil as a carrier. The granulated form, also used in this study, is oil-extracted lecithin. Both choline and inositol have been shown to have lipotropic properties. Many reports have appeared in the literature describing the effect of lecithin, choline or inositol in reducing hepatic lipid accumulation in rats which had been fed large amounts of saturated fats, cholesterol or vitamin B compounds.[11] Both Downs[12] and Kesten and Silbowitz[13] reported the prevention of cholesterol-induced atherosclerosis in rabbits by the simultaneous administration of lecithin. Andrews and Broun[14] obtained similar results with choline. Several reports have appeared describing the lipotropic activity of lecithin in human beings. Gross and Kesten[15] observed a considerable fall in serum cholesterol in a patient with xanthelasma and decided hypercholesteremia following the daily administration of 60 Gm. of soybean lecithin for five weeks. There was a moderate drop with 4 Gm. given daily for sixteen weeks.

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12. Downs, W. G., Jr.: Lecithin in Experimental Arteriosclerosis: A Preliminary Study. Am. Med. **41**:460 (Sept.) 1935.

13. Kesten, H. D., and Silbowitz, R.: Experimental Atherosclerosis and Soya Lecithin, Proc. Soc. Exper. Biol. & Med. **49**:71-73 (Jan.) 1942.

14. Andrews, K. R., and Broun, G. O.: Comparison of the Action of Choline and Lipocaic in the Prevention of Cholesterol Atherosclerosis in the Rabbit, J. Clin. Investigation **19**:786 (Sept.) 1940.

15. Gross, P., and Kesten, B.: Treatment of Psoriasis with Lipotropic Substances Derived from Foodstuffs, Arch. Dermat. & Syph. **47**:159-174 (Feb.) 1943.

Adlersberg and Sobotka,[16] employing 12 to 15 Gm. of either crude or defatted soybean lecithin daily for ten days to thirteen weeks, reported a gradual and progressive fall in the serum cholesterol in 5 patients with xanthomatosis and hypercholesteremia. Paul, Daum and Kemp[17] treated 1 patient with xanthomatosis (type not stated) with choline. The initial total blood fat was 2,208 mg. per hundred cubic centimeters, the phospholipids 1,364 mg. per hundred cubic centimeters and the cholesterol 660 mg. per hundred cubic centimeters. After fifteen days of choline therapy (3 Gm. daily, though the dose was not specifically stated), the total blood fat had decreased to 1,762 mg., the phospholipids to 756 mg. and the cholesterol to 425 mg. per hundred cubic centimeters. In the present study, these observations could not be confirmed. There was no sustained drop in serum cholesterol in any of the 4 patients given 18 to 54 Gm. of crude or 12 to 24 Gm. of defatted lecithin continuously for eight to fifteen weeks.

There have been several reports on the administration of lipocaic to patients with primary (essential) xanthomatosis and hypercholesteremia. Rosenak[18] prescribed for an adult patient 2 Gm. of lipocaic daily for two months and later increased the dose to 3 Gm. for another two months, without any effect on the hypercholesteremia. Comfort, Shepard and Snell,[19] using lipocaic intermittently or continuously for periods up to two weeks and in doses of 2 to 8 Gm., observed no effect on the serum cholesterol levels in an adult with xanthomatous biliary cirrhosis. In the present study there was no clinical improvement, either in the lesions or in the serum cholesterol values in an 11 year old child given 6 Gm. of lipocaic daily for twenty-four weeks and the same amount of pancreatic extract with lipocaic-like properties for the next fourteen weeks.

The decided variability of the plasma lipids in persons with primary (essential) xanthomatosis studied over long periods of time is apparent, but not real. In 2 patients investigated at repeated intervals for forty-seven and forty weeks, respectively (cases 1 and 7), the maximum

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19. Comfort, M. W.; Shepard, V. D., and Snell, A. M.: Xanthomatous Biliary Cirrhosis: Report of a Case, Proc. Staff Meet., Mayo Clin. **16**:374-377 (June 11) 1941.

deviation from the average blood cholesterol was less than 15 per cent (case 5, studied for fifty weeks, is omitted from these calculations because of the obvious reduction of the serum cholesterol apparently due to a diet low in fat and low in cholesterol). These observations agree with the observations recorded by several workers,[20] who reported remarkable constancy of the blood cholesterol of normal adults studied for long periods of time. As pointed out by Weinhouse,[21] the relatively wider fluctuations of the blood cholesterol in persons reported by other workers[22] amounted to approximately 15 per cent when recalculated as deviations from the average. It would appear, therefore, that the blood cholesterol in patients with xanthomatous disease exhibits no greater variations over periods of several months than that observed in normal persons. The apparent wider fluctuations are obviously due to higher levels of blood cholesterol.

SUMMARY AND CONCLUSIONS

In 7 patients with primary (essential) xanthomatosis and hypercholesteremia, the oral administration of vitamin E (d,l-alpha-tocopherol acetate or mixed natural tocopherols) failed to decrease the level of the total plasma lipids, fatty acids and cholesterol.

In 4 patients with primary (essential) xanthomatosis and hypercholesteremia, oil-free or crude lecithin likewise failed to decrease the level of the serum cholesterol.

In 1 patient with primary (essential) xanthomatosis and hypercholesteremia, the ingestion of relatively large doses of lipocaic and pancreatic extract did not diminish the level of the serum cholesterol.

In 4 patients with secondary hypercholesteremia due to various metabolic defects (e.g., diabetes mellitus), vitamin E (d,l-alpha-tocopherol acetate or mixed natural tocopherols) failed to influence the level of plasma cholesterol. In 2 of these 4 patients, there was a sustained reduction in the total plasma lipids and fatty acids without alteration in the plasma cholesterol.

The variations of the serum cholesterol in patients with xanthomatosis studied over many months were no greater than those reported for normal persons; the apparent wider fluctuations were due unquestionably to the elevated levels of serum cholesterol in patients with xanthomatous disease.

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21. Weinhouse, S.: The Blood Cholesterol, Arch. Path. **35**:438-500 (March) 1943.

22. Schube, P. G.: Variations in the Blood Cholesterol of Man over a Time Period, J. Lab. & Clin. Med. **22**:280-284 (Dec.) 1936. Man, E. B., and Gildea, E. F.: Variations in Lipemia of Normal Subjects, J. Biol. Chem. **119**:769-780 (July) 1937.

EFFECT OF PROPHYLACTICALLY ADMINISTERED PENICILLIN ON INCIDENCE OF BACTEREMIA FOLLOWING EXTRACTION OF TEETH

Results in Patients with Healed Rheumatic and Bacterial Endocarditis

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The frequency of bacteremia following the extraction of teeth and its importance in the development of bacterial endocarditis have been established both experimentally[1] and clinically.[2] Since endocarditis is such a serious disease, the introduction of the sulfonamide compounds and antibiotics has been inevitably followed by studies to determine their value in the prevention and eradication of this bacteremia. Although the results obtained by sulfonamide prophylaxis were

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Drs. Georgine Rotman-Kavka, Jay A. Robinson, William W. Zeller and Schneider Spiegel cooperated in the completion of these studies, and Miss Joan Rowe rendered technical assistance.

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encouraging, nevertheless cases of bacterial endocarditis were observed after premedication with the sulfonamide drugs. Because penicillin is superior to sulfonamide compounds in the treatment of endocarditis, it seemed advisable to us to employ this antibiotic in an attempt to prevent the bacteremia which follows dental extraction.

PLAN OF STUDY

Patients who were to have teeth extracted were placed in two groups, one to receive penicillin before operation and the other to serve as a control. In nearly every instance, the patient had been admitted to one of the services of a general hospital for some other illness, and the need for dental extraction was usually incidental. All types of patients were included in the study, except that no one was included who had rheumatic or congenital heart disease or an infectious disease which was likely to be accompanied with bacteremia. There was no selection of patients according to age, color, sex, number of teeth to be extracted or condition of the gums. Patients were not included in the study if they had received a chemotherapeutic or antibiotic agent during the previous twenty-four hours.

The choice of the type and dose of penicillin and of the time of administration in relation to the time of extraction was based on several considerations. We decided to employ a preparation which could be administered simply in the private practice of a dentist or physician, and an amount which would assure a peak concentration in the blood at the time of extraction and maintain an adequate concentration for a maximum period of time. On the basis of previous work, a dose of 600,000 units of penicillin in peanut oil and beeswax[3] given three to four hours before extraction was selected as best satisfying those requirements.

It was our purpose to employ all of the procedures known to decrease the incidence of bacteremia and, at the same time, to utilize measures which would facilitate the growth of any bacteria that reached the blood. Accordingly, we decided to obtain local anesthesia by means of procaine hydrochloride, to which had been added epinephrine hydrochloride in a dilution of 1:25,000, employing infiltration, alone or combined with the conduction method, depending on the location of the tooth. Local infiltration anesthesia has been shown to decrease the incidence of bacteremia.[2c] Feldman and Trace[4] suggested that the use of a local anesthetic causes compression of the blood vessels and lymphatics and minimizes dissemination of any bacteria present. In rabbits, procaine is reported to increase the bactericidal and phagocytic power of the blood and thus to act both as a systemic and as a local barrier to the entrance of organisms into the circulation.[5] Furthermore, epinephrine, by its vasoconstricting action, decreases the possibility of the bacteria gaining access to the blood stream.[2c]

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3. Hirsh, H. L.; Dowling, H. F.; Vivino, J. J., and Rotman-Kavka, G.: Penicillin in Beeswax and Peanut Oil, a New Preparation Which Is Fluid at Room Temperature: Absorption and Therapeutic Use, J. Lab. & Clin. Med. **32**: 34, 1947. One cubic centimeter of this preparation contains 300,000 units of penicillin in refined peanut oil containing 4.8 per cent bleached beeswax, U. S. P.

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5. Villardo, S.: Immunity Phenomena in Procaine Hydrochloride Anesthesia, Gior. di batteriol. e immunol. **20**:1201, 1938.

Two of us (D.H.F. and H.L.H.)[6] have shown previously that the addition of penicillinase to culture mediums to be used for body fluids containing penicillin facilitates the growth of any bacteria present. This enzyme[7] was added to the culture mediums to be used for blood of the patients receiving penicillin, since preliminary tests had demonstrated that penicillinase did not influence the growth of bacteria other than by inactivating the penicillin present.

Studies by several investigators[8] demonstrated that the addition of sodium polyantheolsulfonate ("liquoid") to culture mediums in concentrations of 0.33 to 0.2 per cent favored the growth of organisms present in the blood to be cultured. These investigators expressed the opinion that this compound impaired or destroyed the native antibody present in normal human blood. We employed "liquoid"[9] in the culture medium in a concentration of 0.3 per cent. It was added only to the medium employed for aerobic culture, however, inasmuch as Hoare[10] reported that "liquoid" is unfavorable to the growth of anaerobic streptococci.

Twenty cubic centimeters of blood was taken immediately after the extraction of the teeth, and again, ten and thirty minutes later. Eight to 10 cc. was placed in 30 cc. of culture medium for aerobic culture and an equal amount in a similar medium for culture under anaerobic conditions. In the case of patients receiving penicillin, the remainder of the blood was used for determination of the penicillin concentration. Hirsh, Dowling and O'Neil[11] found that these amounts were the optimal proportions for this purpose. The flasks were incubated at 37 C. Anaerobic conditions were obtained in a museum jar with a lighted candle. The culture flasks were inspected daily, but subcultures were not made for seven days unless there was evidence of growth at an earlier date. Subcultures were made on blood agar plates. Throat cultures were made on blood agar plates on all patients before extraction, and a culture was made from the tooth socket immediately after the tooth was extracted. This was done in order to discover the presence of similar strains in the blood and in the tooth socket or the pharynx. The detailed results are to be published elsewhere.[12]

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6. Dowling, H. F., and Hirsh, H. L.: The Use of Penicillinase in Cultures of Body Fluids Obtained from Patients Under Treatment with Penicillin, Am. J. M. Sc. **210**:756, 1945.

7. Supplied by Schenley Laboratories, Inc.

8. (*a*) Massa, M., and Battistini, G.: Anticomplementary Action and Inhibition of Bactericidal Power of Blood by Sodium Polyanetholsulfonate Used in Hemoculture, Zentralbl. f. Bakt. (Abt. 1) **131**:241, 1934. (*b*) Baiocchi, P.: Contributo allo studio delle batteremie chirurgiche con emoculture comparate: Batteriemia pre-e post-operatoria negli interventi asettici, Gior. di batteriol. e immunol. **21**:63, 1938. (*c*) Von Haebler, T., and Miles, A. A.: The Action of Sodium Polyanetholsulphonate ("Liquoid") on Blood Cultures, J. Path. & Bact. **46**:245, 1938.

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In order to evaluate whether the condition of the mouth or the type of extraction had any influence on the incidence of bacteremia, each of these factors was classified. The state of the oral hygiene of the patients was rated on the basis of the severity of dental caries and gingival disease as follows: (*a*) no apparent disease, (*b*) mild dental caries and/or gingivitis, (*c*) moderate dental caries and/or gingivitis and (*d*) presence of frank pus.

The amount of trauma which accompanied the extraction was indicated by the following operative classification:

Type
1 Tooth loose
2 Plain forceps extraction
3 Extraction requiring the use of elevators
4 Extraction requiring bone surgery

RESULTS

Sixty-five patients were given 600,000 units of penicillin in oil and wax three to four hours before the extraction of teeth, and an equal number of patients who had teeth extracted were not given penicillin and served as controls. The two groups were essentially alike with respect to age, sex and racial distribution. On the basis of the classifications previously outlined, the oral hygiene and types of extraction were comparable for the two groups. The number of teeth extracted from the patients in the control group averaged 2.4 (range, 1 to 11), while for the penicillin-treated group the average was 3.1 (range, 1 to 14).

The varieties of organisms found and the frequency with which they were encountered for the two groups at each time interval are shown in table 1. Since in many instances the same organism was isolated both in the aerobic and in the anaerobic cultures, the total number of positive cultures for the same organism at each time interval is indicated by the figures in the third column for each group. For each time period studied the incidence of bacteremia was higher for the group of patients serving as controls than for the group receiving penicillin. For the time immediately following extraction the incidence was 25

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13. (*a*) Pressman, R. S., and Bender, I. B.: Effect of Sulfonamide Compounds on Transient Bacteremia Following Extraction of Teeth: I. Sulfanilamide, Arch. Int. Med. **74**:346 (Nov.) 1944. (*b*) Bender, I. B., and Pressman, R. S.: Factors in Dental Bacteremia, J. Am. Dent. A. **32**:836, 1945. (*c*) Northrop, P. M., and Crowley, M. C.: Further Studies on the Effect of the Prophylactic Use of Sulfathiazole and Sulfamerazine on Bacteremia Following Extraction of Teeth, J. Oral Surg. **2**:134, 1944.

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TABLE 1.—*Incidence of Positive Cultures Following Dental Extraction*

Organisms	Immediately After Extraction						Ten Minutes After Extraction						Thirty Minutes After Extraction					
	Control Group			Penicillin-Treated Group			Control Group			Penicillin-Treated Group			Control Group			Penicillin-Treated Group		
	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total	Aerobic	An-aerobic	*Total
Alpha and gamma streptococci	17	9	19	7	4	8	5	4	7	2	1	3	1	1	2	0	0	0
Staphylococcus albus	0	1	1	2	1	3	1	3	4	3	1	4	2	1	3	2	2	4
Staphylococcus aureus	1	2	3	0	0	0	1	3	4	1	0	1	0	0	0	1	0	1
Diphtheroids	1	0	1	0	2	2	2	0	2	0	0	0	0	2	2	1	0	1
Neisseria	1	0	1	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0
Other organism	0	0	0	0	0	0	0	0	0	0	2	2	1	0	1	1	0	1
Total	20	12	25	9	8	14	9	10	17	6	5	11	4	4	8	5	2	7

*Total number of different strains; some organisms were found both aerobically and anaerobically.

TABLE 2.—*Number of Patients with Bacteremia Following Dental Extraction**

Organisms	Immediately After Extraction				Ten Minutes After Extraction				Thirty Minutes After Extraction				Total Number of Cultures†				Total Number of of Patients			
	Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group		Control Group		Penicillin-Treated Group	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent‡	Number	Per Cent‡	Number	Per Cent‡	Number	Per Cent
All organisms	22	34	13	20	14	22	10	15	8	12	7	11	44	--	30	--	30	46	24	37
Alpha and gamma streptococci	19	29	8	12	7	11	3	5	2	3	0	0	28	64	11	37	22	34	10	15
Other organisms	6	9	6	9	9	14	8	13	6	9	7	11	21	36	21	63	9	14	16	25

*Some patients had more than one organism in the culture at the same time.
†Positive at all three periods for different organisms (table 1: Six patients in control groups and 2 in penicillin-treated group had same organism at more than one period).
‡Percentage of total number of positive cultures.

for the control series, as compared with 14 for the penicillin-treated patients. For the ten minute interval, the number of cultures yielding pathogens was 17 and 11, and for the thirty minute interval, 8 and 7 respectively.

The total number of patients whose blood was found to contain organisms on culture is shown in table 2. For the time immediately after extraction, the number of patients with blood cultures yielding organisms was 22 (34 per cent) in the control group and 13 (20 per cent) in the penicillin-treated group. The corresponding figures for the ten minute interval after extraction were 14 (22 per cent) and 10 (15 per cent), and those for the thirty minute interval 8 (12 per cent) and 7 (11 per cent), respectively. The apparent discrepancy between the total number of positive cultures and the total number of patients having positive cultures for the first two of the intervals studied is accounted for by the fact that cultures for some patients yielded more than one organism at each of the periods studied. For all the time periods studied, 30 of 65 patients (46 per cent) in the control group were found to have bacteremia, whereas 24 of the 65 (37 per cent) treated with penicillin had bacteremia after operation. These differences are not statistically significant when tested by the chi square method.

Since the alpha and gamma streptococci are the important bacteria in the pathogenesis of bacterial endocarditis, we have divided the patients into those from whose blood alpha and gamma streptococci were isolated and those from whose blood one of the other organisms was cultured (table 2). It is obvious that the differences in favor of the penicillin-treated patients are the result of decreased incidence of bacteremia due to the alpha and gamma streptococci. The incidence of bacteremia for the other organisms was essentially the same for the two groups of patients. When alpha and gamma streptococci alone are considered, the differences between the incidence of bacteremia for the penicillin-treated group and that for the control group for the period immediately following extraction is statistically significant when tested by the chi square method, whereas the differences at the other two periods studied are not statistically significant. The difference between the number of patients (22, or 34 per cent) with bacteremia at any time due to the alpha and gamma streptococci in the control group as compared with the number (10 or 15 per cent) in the penicillin-treated group is also statistically significant. It appears likely, therefore, that penicillin was instrumental in decreasing the incidence of bacteremia due to streptococci but not that due to the other organisms.

In addition to the incidence of bacteremia, the persistence of the various strains isolated was determined. It was found that 6 patients in the control group had positive cultures for the same strain at more

than one time interval, whereas this occurred for only 2 patients in the penicillin-treated group. Because of the small number of cases, this difference is not statistically significant.

An attempt to correlate the incidence of bacteremia in the two groups of patients according to age, sex, race and condition of the gum and teeth revealed no relation of these factors. When the type of operation is considered, a definite increase in the incidence of bacteremia in the more extensive surgical procedures is apparent for both the penicillin-treated and the control group of patients. In the penicillin-treated group, none of the patients with type 1 or 4 extraction had bacteremia. The incidence of bacteremia for extractions of types 2 and 3 was 31 per cent in each group. None of the patients in the control group with a type 1 extraction had bacteremia. Of the patients with extractions of types 2, 3 and 4, 36, 59 and 40 per cent, respectively, had bacteremia. The increase was noted for both the alpha and the gamma streptococci, as well as for the other organisms isolated. It is apparent that penicillin reduced the incidence of bacteremia following more extensive surgical procedures.

In those patients treated with penicillin from whose blood cultures organisms were isolated at any period, the concentration of penicillin in the blood was determined for that period. In addition, the in vitro sensitivities of most of the bacteria isolated were determined. In the case of the alpha and gamma streptococci, the concentrations of penicillin in the blood were always greater than the in vitro sensitivity of these organisms. Of the other organisms, about one-half were sensitive to less and the others resistant to more than the penicillin concentration present in the blood at the time interval at which they were found. None of the patients in this series had any complications as a result of the dental extractions other than the transient bacteremia.

PATIENTS WITH HEALED ENDOCARDITIS

Seven patients with rhuematic or healed bacterial endocarditis were given penicillin before the extraction of teeth on 11 occasions. These patients were not included in the series because they represented cases specially selected for penicillin therapy. In the case of 4 of the extractions, the patients received 25,000 units of penicillin one hour before extraction and 25,000 units every three hours thereafter, for seven doses. In the remaining 7 extractions, 600,000 units in 2 cc. of oil and wax was given three to four hours before the extraction. In 4 instances, bacteria were cultured from the specimen of blood taken immediately after extraction. In 3 instances the organism was Streptococcus viridans (alpha type) and in the fourth Staphylococcus albus. All of

these patients made an uneventful recovery and have been followed for periods of from six months to two years. The strain of Staph. albus and one of the strains of Str. viridans were sensitive to less penicillin than was found in the blood at that time, while the other two strains were resistant to the concentrations present in the blood.

COMMENT

The desirability of eliminating, or even diminishing, the frequency of one of the causes of bacterial endocarditis is obvious. The effect of sulfonamide prophylaxis on the incidence and persistence of bacteremia following the extraction of teeth has been inconclusive. Some reports have indicated that sulfonamide compounds were ineffective, while other investigators[13] have stated that these drugs either decreased the incidence of bacteremia or caused a prompter disappearance of the organisms from the blood. Not only are the reports contradictory, but it is difficult to evaluate the results adequately, as in most of the series either there was no control group or the investigators failed to include para-aminobenzoic acid in their culture mediums. The necessity for the use of para-aminobenzoic acid in the culture mediums to be used for body fluids containing sulfonamide drugs has been established.[14] Furthermore, the fact that sulfonamide compounds under most conditions are only bacteriostatic would make it appear unlikely that these drugs could effect a more rapid disappearance of organisms from the blood over a ten minute period than has been reported.[13a, b]

The present study was undertaken to evaluate the use of penicillin before dental extraction. We gave penicillin prophylactically to 65 unselected patients and observed the incidence of bacteremia after tooth extraction in these patients as compared with the control group of 65 patients who were not given penicillin. When all the organisms cultured from the blood are considered, it is apparent that penicillin did not significantly reduce the incidence of bacteremia. It should be noted, however, that only 53 per cent of all the organisms isolated were alpha and gamma streptococci. The incidence of organisms other than alpha and gamma streptococci is higher than most investigators have reported. We are of the opinion that these organisms were actually present in the blood. Similar organisms were frequently isolated from the cultures made from the throat and tooth sockets, and it is conceivable that they, as well as the alpha and gamma streptococci, could gain access to the blood through the open wound. All the specimens of blood were obtained by 4 persons, and strict measures were observed for minimizing contamination. Furthermore, in the course of routine work done concomitantly in the same laboratory, hundreds of cultures of blood

taken by numerous persons under less ideal conditions were examined. In all these cultures the number of bacteria obtained as contaminants was exceedingly low. In any event, the organisms other than the alpha and gamma streptococci isolated from the blood cultures are of little siginficance in the pathogenesis of bacterial endocarditis.

If alpha and gamma streptococci alone are considered, it is observed that 600,000 units of penicillin in wax and oil, given three to four hours before dental extraction, reduced the incidence of bacteremia for the penicillin-treated patients as compared with that for the controls immediately after extraction and ten and thirty minutes later. The decreases for the period immediately after extraction and for the total number of patients who had bacteremia at any time were statistically significant.

Glaser and his associates[15] recently reported a study similar to ours in which 40 patients were given large doses of penicillin over a twenty-four hour period before extraction and an equal number served as controls. Blood was taken for culture before and immediately after extraction. Sixty per cent of the patients were found to have alpha or gamma streptococci in the postextraction culture, whereas the incidence was only 40 per cent in the penicillin-treated group. In the control group the alpha streptococci predominated, whereas in the penicillin-treated group the gamma streptococci were found more frequently. In patients with normal gums the use of penicillin did not result in a significant decrease in the incidence of bacteremia after the extraction of teeth. On the other hand, in the patients with gingivitis or pyorrhea the dosage schedule of penicillin employed resulted in a definite decrease in the incidence of bacteremia. These investigators concluded that in patients with rheumatic or congenital heart disease penicillin should be given in large doses for at least twenty-four hours before extraction and should be continued for two to three days thereafter. In patients with normal gums the penicillin may be given before extraction and continued for the same period.

It is interesting to speculate how penicillin prevents the bacteremia following dental extraction. There appear to be two possible explanations. One is that the presence of penicillin in the blood inhibits or kills the organisms after they enter the blood. The other explanation is that penicillin inhibits the growth of bacteria in the gums and in the mouth and throat and thus reduces the number of organisms available for entrance into the blood through the wound. It is probable that both mechanisms operate. A diminution in the number of bacteria in the vicinity of the wound by the use of penicillin before extraction would explain the lower percentage of bacteria present immediately after extraction among the patients who received this antibiotic prophylactically.

This mechanism might also explain the rapid disappearance of the bacteria which entered the blood, since it may be presumed that when bacteria gained access at all they were present in smaller numbers. On the other hand, it is quite likely that the penicillin present in the blood inhibited their multiplication and thus contributed to their rapid disappearance. Unfortunately, we did not make pour plates to determine the number of organisms present in the blood.

Since the bacteremia following dental extraction is of such importance, we believe that certain principles in the management of patients with known rheumatic or congenital heart disease contemplating dental extractions are worthy of emphasis. Patients who are to have extractions should be questioned carefully concerning a previous history of rheumatic fever, chorea, joint pains, growing pains, unexplained periods of fever, frequent sore throats, scarlet fever or any manifestation of a rheumatic diathesis. In the presence of a suggestive, and certainly with a definite, history of rheumatic fever, the patient should be examined for the presence of valvular heart disease before having the dental work undertaken. Patients with a history of cardiac difficulties, such as dyspnea or cyanosis, indicative of congenital heart disease should be similarly managed.

The present study, in conjunction with that of Glaser and his associates, indicates that the incidence of bacteremia caused by alpha and gamma streptococci can be significantly reduced by the use of penicillin before extraction. The optimal dose and time of administration remain to be worked out. On the basis of present knowledge, it seems to us, that the best procedure would be one that assured the presence of penicillin in the gums and adjacent tissues for twenty-four hours before extraction, a peak concentration of penicillin in the blood during and immediately after the extraction and a bactericidal concentration in the blood for at least twenty-four hours after extraction. A practical program which would accomplish this objective would consist of an injection of 300,000 units of penicillin in wax and oil (or a similar preparation) about twenty-four hours before extraction was contemplated. Three to four hours before the extraction an additional dose of 600,000 units of penicillin in wax and oil should be administered.

On the basis of previous investigations, extractions performed by simple elevator-forceps technic, with local infiltration anesthesia induced with procaine and epinephrine, offer the best means of reducing the incidence of bacteremia. Although we were unable to correlate the incidence of bacteremia with the number of teeth extracted, there was a definite correlation between the severity of the surgical procedure and the incidence of bacteremia. Therefore, in patients with rheumatic and congenital heart disease, any manipulative procedure involving the gums and teeth is to be avoided if possible.

SUMMARY

Sixty-five patients requiring dental extractions were each given 600,000 units of penicillin in wax and peanut oil contained in 2 cc. of the mixture three to four hours before extraction, while 65 patients were not given penicillin and served as controls. Extraction was accomplished by the elevator-forceps technic, local infiltration anesthesia being induced with procaine and epinephrine. Blood cultures in duplicate were obtained immediately and ten and thirty minutes after extraction, incubated both aerobically and anaerobically and studied for the presence of bacteria.

When all the organisms isolated were considered, 46 per cent of the patients in the control group and 37 per cent of the patients in the penicillin-treated group were found to have bacteremia. When alpha and gamma streptococci alone were considered, a statistically significant reduction in the incidence of bacteremia, from 34 to 15 per cent, was observed with the use of penicillin.

Six patients in the control group had positive cultures for the same organism at more than one of the periods studied. Only 2 patients in the penicillin-treated series had bacteremia at more than one period.

The incidence of bacteremia could not be correlated with age, sex, race, state of oral hygiene or number of teeth extracted. The number of positive cultures was greater, however, the more extensive the surgical procedure.

Seven patients with healed rheumatic or bacterial endocarditis had dental extractions on 11 occasions, with penicillin administered prophylactically. A transient bacteremia occurred in 4 patients.

A plan of prophylaxis is suggested for use preceding dental extraction in patients with rheumatic and congenital heart disease.

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ADDISON'S DISEASE COMPLICATED BY TOXEMIA OF PREGNANCY

Review of the Literature

MONROE COHEN, M. D.
BROOKLYN

Before the discovery of potent adrenal cortex preparations, the maternal mortality in Addison's disease complicated by pregnancy was 35 per cent among the 20 reported cases. Some case reports are brief, but in most instances the diagnosis of adrenal disease was proved at autopsy Therapeutic abortions were uniformly fatal, and one third of the fetuses died at term delivery.[1]

From 1930 to 1939, 8 cases, with a 25 per cent mortality, were reported. In 4 cases the pregnancies went to term and the patients survived, and in 2 cases therapeutic abortions were successful. Uncontrollable vomiting leading to adrenal crisis caused the death of 1 patient in the second month of pregnancy, and premature labor terminated in the death of another.[2]

From the Department of Medicine, Long Island College of Medicine Division, Kings County Hospital.

1. Davey, N. F.: Case of Complete Disorganization of Both Supra-Renal Capsules Without Discoloration of the Skin, M. Times & Gaz. **18**:30, 1859. von Roten, J.: Kasuistik zur Frage des Morbus Addisonii und Gravidität, Inaug. Dissert. (Basel), Sarnen, L. Ehrli, 1915. Fitzpatrick, G.: Addison's Disease Complicating Pregnancy, Labor or the Puerperium, Surg., Gynec. & Obst. **35**:72, 1922. Fruhinsholz, A.: Fatal Suprarenal Syndrome of the Addisonian Type Connected with the Puerperal Condition, Gynéc. et obstét. **12**:437, 1925. Gustafsen, P., cited by Crabtree, E. G.: Urological Diseases of Pregnancy, Boston, Little, Brown & Company, 1942, p. 369.

2. Garcia, F. H.: Pregnancy and Addison's Disease, Med. ibera **2**:391, 1931. Perkins, P. A.: Addison's Disease and Pregnancy, J. A. M. A. **99**:1500 (Oct. 29) 1932. Bachner, F.: The Problem of Interruption of Pregnancy in Addison's Disease, Zentralbl. f. Gynäk. **56**:1039, 1932. Tapfer, S.: Pregnancy and Addison's Disease, Wien. klin. Wchnschr. **47**:1043, 1934. Thaddea, S.: Relationships Between Adrenal Cortex and Sex Glands, Ztschr. f. Geburtsh. u. Gynäk. **110**:225, 1935. Eng, H.: Fluctuation Between Sex Hormones and Other Endocrine Organs: Secretion of Sex Hormones in a Patient with Adrenal Insufficiency, Klin. Wchnschr. **14**:6, 1935. Stohr, R.: Addisonism in Pregnant Women, Zentralbl. f. Gynäk. **63**:2599, 1939.

Since 1940 there were 15 reported cases, and 7 more have been available to us for study. In 18 of the 22 cases the pregnancy went to term, with 2 deaths. The fact that both deaths occurred in Brooklyn and were unreported makes it likely that few fatal cases are being reported. One of the patients died of a ruptured uterus during a low forceps delivery.[3] The other survived cesarean section and died of acute pulmonary edema on the third day.[4] Therapeutic abortions terminated the pregnancy in the remaining 4 cases; 2 of the patients died, 1 of septicemia and the other of adrenal crisis. The total mortality in this period was 18 per cent. Only 3 fetal deaths after term deliveries are mentioned since 1930, and 2 were unrelated to Addison's disease (tables 1 and 2).

The case here reported is the first to be complicated by preeclamptic toxemia; both mother and child left the hospital in excellent health.

REPORT OF A CASE

A 17 year old white school girl was admitted to the Kings County Hospital in June 1940 because of diffuse abdominal pain, vomiting, anorexa, considerable asthenia, a loss of weight of 30 pounds (13.6 Kg.) and pigmentation of the skin. She appeared extremely ill. The blood pressure was 74 systolic and 40 diastolic, and there was pronounced pigmentation of the skin and the mucous membranes. Roentgenologic study of the chest revealed small exudative tuberculous lesions at both apexes. She responded to infusions of isotonic sodium chloride solution, but later suffered a typical addisonian crisis during a chloride excretion test. After a stormy course, she was eventually given a house diet with 6 Gm. of added salt and 5 mg. of desoxycorticosterone acetate daily. She did well on this regimen, gradually gained weight and maintained a blood pressure of 120 to 130 systolic and 70 to 80 diastolic. Study of the lungs at intervals disclosed stationary and inactive lesions. In November 1940, 5 pellets of 125 mg. of desoxycorticosterone acetate were implanted in the patient. Seven months after her admission she was discharged from the hospital in good condition, having gained 26 pounds (11.8 Kg.). There was a tendency toward edema formation, and the salt in the diet was restricted.

Because of loss of weight and the fall in blood pressure, 5 pellets of 50 mg. of desoxycorticosterone were implanted in August 1942. In December 1943, 3 pellets of 125 mg. were implanted after the patient's condition had been well controlled with the administration of 3 mg. daily. Four pellets of 125 mg. were implanted on June 1, 1945, and except for mild edema of the hands and feet for several months she felt well.

Complaining of weakness and nausea of one week's duration, the patient was readmitted to the hospital on Feb. 19, 1946, when it was learned that her last normal menstrual period had occurred on Dec. 19, 1945. Examination revealed a six week intrauterine gestation. The blood pressure was 100 systolic and 68 diastolic, the hemoglobin 12.5 Gm. per hundred cubic centimeters and the white blood cell count 8,000, with a normal differential count. The urine was normal,

3. Unreported case, Cumberland Hospital, 1941.

4. Unreported case, Long Island College Hospital, 1946.

the blood sugar was 92 mg. per hundred cubic centimeters and the uric acid 3.9 mg. A roentgenogram of the chest showed calcific deposits in the right lower pulmonary fields. Adrenal studies showed no calcification. With control of diet, infusions of dextrose and sodium chloride and adrenocortical therapy, the nausea and vomiting disappeared and the patient was discharged to the antepartum clinic.

TABLE I.—*Cases of Addison's Disease and Pregnancy Since 1940*

Date	Author	Comment
1941	Unreported[3]	Death during delivery from ruptured uterus; low forceps used; stillbirth; atrophic adrenals at autopsy
1943	Samuels, L. T.; Evans, G. T., and McKelvy, J. L.: Endocrinology **32**:422, 1943.	Uneventful pregnancy; symptoms of Addison's disease returned after delivery; 17-ketosteroids rose in last trimester
1945	Sheldon, D. E.: Am. J. Obst. & Gynec. **42**:269, 1945.	Term delivery; mother and infant survived; moderate adrenal crisis on third day
1945	Van Zwanenberg, J.: St. Barth. Hosp. J. **49**:31, 1945.	Survival of 1 patient after term delivery; another patient died 3 days after hysterotomy and sterilization at the fourth month
1946	Valenzi, A.: Clin. ostet. **38**:459, 1946.	Normal delivery at term, with live baby; death in 2 months, not associated with pregnancy; autopsy revealed Addison's disease
1946	Murphy, A. P.: Proc. Roy. Australasian Coll. Phys. **1**:69, 1946.	Labor induced as patient was 3 weeks past term; easy, rapid, uneventful labor; stillbirth due to cord loops around neck
1946	Simpson, S. L.: Proc. Roy. Soc. Med. **39**:511, 1946.	Two pregnancies without complications in 1 patient; survival of both infants
1946	Unreported[4]	Death from acute pulmonary edema on third day after cesarean section; live baby
1946	Cohen, M.	Survival of mother and baby after complication of preeclampsia
1947	Thorn, G. W.; Dorrance, S. S., and Day, E.: Ann. Int. Med. **16**:1053, 1942.	4 patients have had six term pregnancies, with favorable outcomes. Adrenal insufficiency developed in 1 during pregnancy, crisis was precipitated by delivery in 2, and pigmentation increased in 2 after termination of the pregnancy; 1 patient died of septicemia after a therapeutic abortion. No toxemia or hypertension in any case.
1947	Loeb, R. F.: Personal communication to the author.	Of four pregnancies, one was uneventful. Hypertension developed in 1 patient in the last two months of pregnancy, without significant albuminuria, and was attributed to excess desoxycorticosterone acetate and salt; infant died of unrelated condition. One hysterectomy was done in the fifth month for reasons unrelated to the Addison's disease. One pregnancy was terminated at the second month because of recurrent hypoglycemia. All patients survived.

However, the symptoms returned, and the patient lost weight, and she was readmitted to the hospital on April 2, 1946. She was given 3 Gm. of salt daily, added to a regular diet, and 2 mg. of desoxycorticosterone acetate intramuscularly, for the pellets were beginning to lose their effect. The serum sodium content was 324 mg. per hundred cubic centimeters, potassium 19 mg., chloride 590 mg., sugar 61 mg. and the hemoglobin content 9 Gm. It was found necessary to increase the daily injections of desoxycorticosterone to 5 mg., for on this dosage the patient's condition appeared well balanced, and she gained an average of 1 pound (0.5 Kg.) per week and maintained a blood pressure of 100 to 110 systolic and 60 to 65 diastolic. The hematocrit value ranged from 32 to 35, the hemoglobin rose to 11 Gm. and chemical studies of the blood showed little change. The blood protein content was 5.7 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.8. Severe postural hypotension was present, which improved with elevation of the head of the bed and with avoidance of sudden changes in posture. After her discharge from the hospital in June, medication was given and the weight and blood pressure were taken daily by a visiting nurse and weekly at the clinic.

With an estimated date of confinement for Sept. 26, 1946, the patient was readmitted on September 5 for closer observation. Her general condition was good; the blood pressure was 124 systolic and 90 diastolic, the weight 125½ pounds (57 Kg.), the urine normal and the hematocrit value 34.

TABLE 2.—*Maternal Mortality in Addison's Disease and Pregnancy*

Date	Number of Pregnancies	Deaths			Mortality Due to Pregnancy%
		Before Term	At Term or During Puerperium	Weeks or Months After Puerperium*	
1859 to 1930	20	4	3	7	35
1931 to 1939	8	2	0	0	25
1940 to 1947	22	2	2	1	18

*These figures are not included in the statistics on mortality due to pregnancy.

On September 22 the blood pressure rose to 138 systolic and 80 diastolic and fluctuated between 120 and 135 systolic and 90 and 106 diastolic for the next week. A mild pitting edema of the feet, ankles and hands developed, associated with albuminuria (3 plus) and a gain of 3½ pounds (1.5 Kg.) in weight. The dosage of desoxycorticosterone was reduced and finally discontinued and the salt intake limited to 3 Gm. daily. After an initial dose of 30 cc. of adrenal cortex extract (Upjohn), 5 cc. of lipoadrenal extract (Upjohn) was given daily. The blood protein content was 5.2 Gm., the serum albumin 3.1 Gm., the globulin 2.1 Gm. and the uric acid 3.8 mg. per hundred cubic centimeters. The urinary 17-ketosteroids measured 3.6 mg. in twenty-four hours while the patient was on this regimen.

During the next two weeks the blood pressure ranged between 130 and 144 systolic and 90 and 104 diastolic, the edema persisted and the weight increased by 3 pounds (1.3 Kg.). The urinary albumin level reached 4 Gm. in twenty-four hours, and the fundi showed arteriovenous nicking. From October 16 to 19 aqueous adrenal extract was given to conserve the supply of lipoextract (chart 1).

Because of no evidence of the onset of labor and of the persistence of the toxemia it was decided to induce labor by rupturing the membranes and giving alphahypophamine in 1 minim doses on October 19. After the onset of fairly strong contractions, the blood pressure remained at approximately 150 systolic and 105

diastolic. Sixteen hours later it rose to 170 systolic and 120 diastolic and then to 188 systolic and 128 diastolic during contractions. Five per cent dextrose in water was given slowly intravenously. The cervix became fully dilated eighteen hours after the rupture of the membranes, and under local anesthesia an episiotomy was performed and low forceps delivery of an 8 lb. 4 oz. (3.7 Kg.) living male infant in good condition was effected. The blood loss was 500 cc. Within twenty minutes after delivery the blood pressure fell to 126 systolic and 106 diastolic and the pulse rate rose to 140. Two hundred and fifty cubic centimeters of plasma was given rapidly, and the pressure rose to 145 systolic and 105 diastolic and the pulse fell to 94. Five cubic centimeters of lipoextract was given and during the next twelve hours 1,500 cc. of 5 per cent dextrose in water. The patient remained in fair condition.

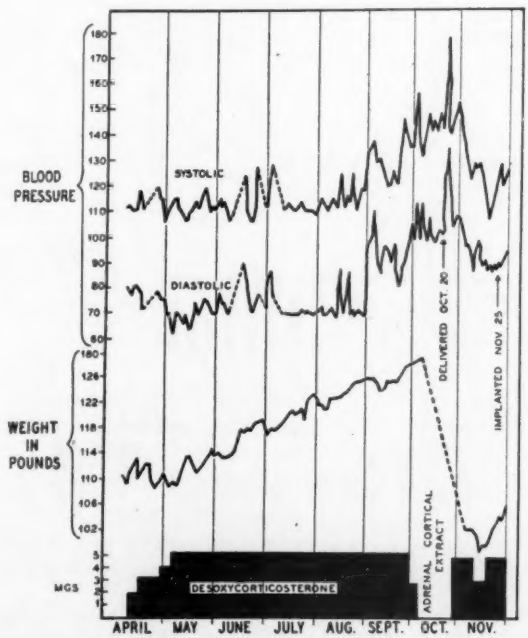

Chart 1.—Blood pressure, weight and therapy during pregnancy and puerperium in patient with Addison's disease.

During the next three days, the patient received 2 to 2½ liters of 5 per cent dextrose in water and 5 cc. of lipoadrenal extract daily with a diet containing 3 to 5 Gm. of salt. There was a decided diuresis immediately after delivery, and thereafter the urinary output exceeded the fluid intake. The hematocrit reading gradually fell to 24 and the hemoglobin to 6.5 Gm. per hundred cubic centimeters by the third day, and two blood transfusions of 500 cc. each were given on the third and fifth days, which brought the hemoglobin level to 10.5 Gm. and the hematocrit reading to 31. Blood pressures ranged between 154 and 132 systolic and 106 and 94 diastolic, the edema disappeared and the urinary albumin level

decreased to 1 or 2 plus. One week after delivery hormone therapy was discontinued, but it was reinstituted after two days when the patient suddenly became weak. She was given an infusion of sodium chloride solution, cortical extract and desoxycorticosterone, and she improved (chart 2).

After this episode 5 mg. of desoxycorticosterone was given daily, with the patient on a regular diet and 3 Gm. of extra salt. After ten days the blood pressure ranged between 110 and 120 systolic and 74 and 84 diastolic, with a hematocrit value of 38 and a hemoglobin content of 13 Gm. The dose of desoxycorticosterone was reduced to 3 mg., but after one week's trial it was raised to 5 mg. again as

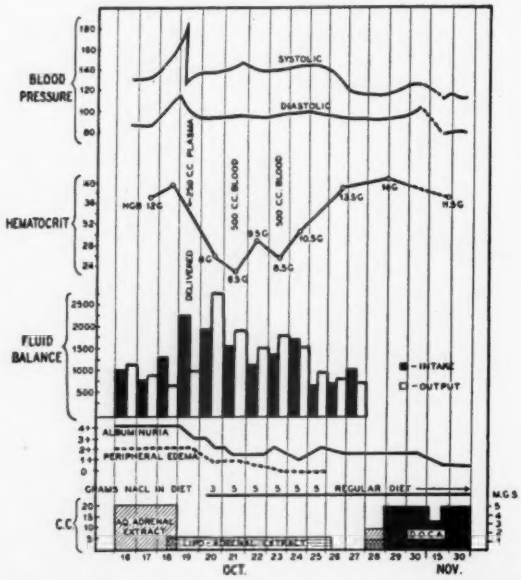

Chart 2.—Blood pressure, hematocrit reading, hemoglobin content, fluid balance, edema, albumin level and therapy at time of delivery and during puerperium.

the patient lost 4 ponnds (1.8 Kg.) in weight, and the blood pressure fell to 96 systolic and 74 diastolic. With the latter dosage, the patient felt well and maintained a blood pressure of 108 to 122 systolic and 78 to 84 diastolic (chart 1).

One month after delivery she was discharged from the hospital, after implantation of 4 pellets of desoxycorticosterone acetate of 125 mg. each. The urine continued to have a trace of albumin. The hematocrit value was 37, the hemoglobin 11.5 Gm. per hundred cubic centimeters and the blood pressure 122 systolic and 84 diastolic. The baby was also discharged in good condition, appearing normal in all respects. One year later the patient and the baby were living and well.

COMMENT

Preeclampsia in Addison's disease has not been reported. The diagnosis in this case was established when hypertension, edema and sig-

nificant albuminuria occurred which did not change after administration of desoxycorticosterone was stopped. The salt intake had to be restricted to 3 Gm. daily, and whole extract was given. Labor was induced because of the prolonged toxemia, with risk of permanent renal damage. The mechanism of toxemia is obscure, but it is of interest that it can occur in the presence of poorly functioning adrenal glands. In this case, the amount of desoxycorticosterone acetate required formerly was relatively low, 3 pellets of 125 mg. having kept the patient well for almost eighteen months two years before her pregnancy. However, 4 pellets of 125 mg. implanted six months prior to the patient's pregnancy lasted ten months, and it is believed that this patient's adrenals produced almost no sterone since the 17-ketosteroid content was low and the amount of desoxycorticosterone acetate required during pregnancy and after delivery was 5 mg. per day. None was given from the onset of toxemia until the blood pressure fell ten days after delivery.

In a consideration of the hazards of pregnancy complicating Addison's disease, it may be noted that the normal pregnant woman has a tendency to have hypoglycemia. In the presence of Addison's disease, when carbohydrate metabolism is more impaired, there is reason for concern when there is hyperemesis in the first trimester. It is often difficult to prevent severe hypoglycemic states and adrenal crisis. Excessive vomiting requires adequate sodium chloride solution, dextrose and hormone therapy. Whole gland extract and frequent high carbohydrate feedings may control hypoglycemic episodes. Since term pregnancy offers a more favorable prognosis than therapeutic abortion, the patient should be allowed to go through the early phase of pregnancy unless some unusual or hazardous complication arises.

It has been stated that patients with Addison's disease tolerate the later months of pregnancy well because of the cortin-like action of the sex hormones, whose titer rises considerably as pregnancy advances. Their sodium-retaining action, especially that of progesterone, has been well demonstrated by the prolonged survival of adrenalectomized animals during pregnancy and heat without the use of cortical hormone. A striking and extended fall in excretion of sodium occurs in normal dogs given progesterone or estradiol.[5]

The fetal adrenals have been credited with supplying adrenal hormones for the maternal welfare. Houssay has recently demonstrated that the adrenals of the litter of adrenalectomized rats weigh more than those in the litter of normal mothers. Atrophy of the fetal adrenals did not occur when the mothers were given large doses of

5. Thorn, G. W., and Harrop, G. A.: Sodium-Retaining Effect of Sex Hormones, Science **86**:40, 1937.

desoxycorticosterone.[6] However, studies on the adrenal corticoids, the fractions related to carbohydrate metabolism, show them to be increased in the first and last months of normal pregnancy. Since the infant's urine during the first few days after birth shows no corticoid activity, it is doubtful that the fetal adrenals contribute to the maternal hormone requirements.[7]

Most patients with Addison's disease do well after the early months of pregnancy. Pigmentation often appears lighter, and the general condition is good in the large majority as the pregnancy goes on to term. During this time the blood pressure, weight and hematocrit value are probably the most important signs to follow. Implantation of pellets is contraindicated, for the hormonal requirements might change in the last few months.

The danger of adrenal crisis is ever present during labor and the puerperium, for the loss of blood during delivery, the sudden deprivation of the sex hormones, the excretion of salt with excessive sweating during labor and the changes in blood volume with postpartum diuresis all combine to form an unpredictable, fluctuating physiologic state. Laboratory tests are of little value in these circumstances, and the clinical condition of the patient is the best guide to therapy. Adrenal cortex extract is given when labor starts and continued until the patient is well out of danger. Adequate intake of dextrose will prevent hypoglycemic reactions. Delivery should be from below, with local anesthesia, episiotomy and forceps to hasten the second stage of labor. Sodium chloride solution is needed if the labor is prolonged and sweaty and blood if appreciable hemorrhage occurs. Implantation of pellets is contraindicated until at least one month after delivery.

SUMMARY

1. Before 1930, 35 per cent of reported cases of pregnancy in Addison's disease resulted in maternal death before the end of the puerperium. In the 8 reported cases between 1930 and 1940 the maternal mortality was 25 per cent.

In a series of 22 cases of pregnancy in Addison's disease reported in the literature or from stated sources since 1940, only 4 deaths occurred during pregnancy and the puerperium, a mortality of 18 per cent. There were four operative interruptions in this series, accounting for 2 deaths. One death was due to uterine rupture during delivery and 1 occurred

6. Houssay, B. A.: The Influence of Suprarenal Insufficiency on Mother and Fetus During Pregnancy, Rev. Asoc. méd. argent. **60**:83, 1946.

7. Venning, E. H.: Adrenal Function in Pregnancy, Endocrinology **39**:203, 1946.

from pulmonary edema three days after cesarean section and liberal infusions of sodium chloride solution. No death due to crisis occurred in 16 cases in which the pregnancy went to term.

3. More careful obstetric management may further decrease the mortality from pregnancy in Addison's disease.

4. Toxemia of pregnancy may occur in Addison's disease in the absence of effective depots of desoxycorticosterone acetate in the body. Restriction of salt intake, administration of cortical extract and discontinuance of the use of desoxycorticosterone were effective therapeutic measures in the reported case until ten days after delivery, when acute symptoms of Addison's disease recurred. The amount of desoxycorticosterone acetate required after pregnancy seemed slightly greater than that required during the previous five years of the patient's disease.

The Obstetrical Department, Long Island College of Medicine Division, cooperated in the study and in the reporting of this case, and Dr. Andrew M. Babey supplied several references to case reports not cited previously.

Book Reviews

Cor pulmonale: I. Congreso Nacional de Cardiologia, II. Ponencia. By J. Codina-Altés, M.D. Pp. 206, with 72 illustrations. Madrid: Libreria Editorial, Cientifico Médica Española, 1944.

This book is an exhaustive study of cor pulmonale, with references to all American literature but which include British, French and German references. In addition to a well organized and excellent condensation of the literature, Dr. Codina-Altés includes his personal observations on 97 cases.

The author discusses the subject in respect to etiology, pathogenesis, clinical, radiologic and electrocardiographic findings, clinical course, diagnosis and treatment and includes separate discussions of acute and subacute cor pulmonale. Charts and roentgenograms from many of his own cases are appended.

The Management of Obesity. By Louis Pelner, M.D. Price, $3. Pp. 144. New York: Personal Diet Service, 1946.

In this book both the endocrine aspects of obesity and the practical management of the condition of the obese patient are discussed. Many physicians do not agree with Engelbach's classification of the hypogonad, castrate, adiposogenital and pituitarothyroid types of obesity. Not all physicians will agree with the statement that "The patient should always be given a diet consisting of about 1,000 calories," since many physicians prescribe diets containing fewer calories.

Considerable attention is given to the use of drugs in the treatment of obesity. The food tables and outlines of diets consisting of 1,000, 1,200 and 1,500 calories are satisfactory. This small volume with references and index will be helpful to many physicians.

Recent Advances in Clinical Pathology. By S. C. Dyke, M.D. and others. Price, $5.50. Pp. 468. Philadelphia: The Blakiston Company, 1947.

It has become increasingly difficult for any one person to present adequately the advances in the various aspects of clinical pathology. In preparing this text on the "recent advances in clinical pathology," sponsored by the European Association of Clinical Pathologists, the editor has enlisted the aid of section editors for the four divisions of bacteriology, biochemistry, hematology and histology. These in their turn have secured the services of those best fitted to present the advances in each of their special fields. The result has been a compact but comprehensive volume, of great value not only to clinical pathologists but also to practicing physicians.

Essentials of Medicine. By Charles P. Emerson Jr., M.D., and Jane Elizabeth Taylor, R.N. Fifteenth edition. Price, $3.50. Pp. 688. Philadelphia: J. B. Lippincott Company, 1946.

The appearance of a fifteenth edition of this standard work indicates that many generations of instructors in schools of nursing have found it to be a satisfactory textbook. Economy in print and margins now makes it possible to condense an immense amount of information in an octavo volume. The general format and the many diagrams, photograps and colored plates are excellent features, and we have no doubt that the book will continue to be a leader in the field of nursing education.

Methods of Diagnosis. By Logan Clendening, M.D., and E. H. Hashinger, M.D. Price, $12.50. Pp. 868, with 143 illustrations. St. Louis: The C. V. Mosby Company, 1947.

Dr. Logan Clendening was a talented physician. Among other gifts he had an ability to express his ideas in writing picturesquely, entertainingly and with great vividness. He must have done his full share in the preparation of this book, for his personality and literary style are impressed on many of its pages.

The volume is divided into two distinct parts. The first deals with methods of clinical diagnosis and the second with laboratory and other special procedures.

The latter part is fairly orthodox and is a well balanced text which meets ordinary standards. The first part is more interesting because here Dr. Clendening's personal touches are so apparent. He attempts to tell any medical student or physician how to make a diagnosis: first by analysis of what the patient says, next by physical examination—and its proper technic is described carefully—and finally by the correct interpretation of what the laboratory may reveal. Fitted into this general pattern to give it color are bits of medical history, anecdotes, a great deal of common sense and a lot of clinical information based on experience. On the whole, therefore, one is likely to read the chapters in this part of the book not only for the information which they contain but also because their perusal is an enjoyable experience in medical literature.

The illustrations, in part diagrammatic and in part photographic, are excellent. The words "I" and "my" appear frequently, and many statements are dogmatic. This introduces a personal element, which is not unpleasant; one feels as if Dr. Clendening had prepared each chapter for one's special benefit.

Here is an unusual textbook. Only a rare reader will find it tedious.

Quimioterapia antiinfecciosa en medicina interna (sulfamidas-penicilina). Presented at the second Congress of the Society of Internal Medicine in Argentina, October 1944. Pp. 497. Buenos Aires: "El Ateneo," 1945.

This book is a collection of papers on the subject of anti-infectious chemotherapy in internal medicine, presented in October 1944 before the Society of Internal Medicine of Buenos Aires on the occasion of its second congress. Among the numerous authors contributing to this work are well known authorities of Argentina, Uruguay, Brazil and the United States.

The first group of papers was presented at the congress and includes an introduction to the pharmacology of the sulfonamide compounds. This portion is devoted to the uses of the latter in the following infectious processes: acute and chronic respiratory diseases, septicemia, generalized infections of gynecologic or obstetric origin, rheumatic fever and pericardial conditions, nephropathies and urinary infections. Considerable mention is made of the pharmacologic qualities of penicillin and the clinical observations on its use.

The second group of papers includes discussions of the chemotherapeutic treatment of bacterial asthmas and actinomycosis and of the clinical uses of tyrothricin. Studies are presented on the analgesic and anesthetic properties of sulfathiazole. These papers were communicated to the meeting and not read before it.

Some of the concepts presented have changed greatly in interpretation during the last two years. However, the large amount of basic research reviewed in most of the articles is of great value to the reader interested in the thorough investigation of this subject.

Surgical Pathology. By William Boyd, M.D. Sixth edition. Price $10. Pp. 858, with 530 illustrations including 22 in color. Philadelphia: W. B. Saunders Company, 1947.

The ARCHIVES is glad to welcome this edition. The book first appeared twenty-two years ago and ever since has reappeared in new editions every four or five years. During its life, its size and price have remained about the same despite new knowledge and higher living costs, which speaks for the artfulness of its writer. Its illustrations—which reviewers always tend to compliment—have increased in number and interest.

The author believes that something can be learned from a study of surgical pathology that cannot be learned through general pathology. He defends this belief in an agreeable style that makes for easy reading. The first five editions of this particular text have been popular both with students and with their teachers. It is safe to predict that the sixth will have an equally successful career.

Atlas of Cardiovascular Diseases. By Irving J. Treiger, M.D. Price, $10. Pp. 180, with 244 illustrations. St. Louis: The C. V. Mosby Company, 1947.

This folio volume contains on each right hand page roentgenograms, electrocardiograms and photographs of gross specimens and on the left an abstract of the case history. The material is well selected and concisely presented, and the entire range of important cardiac lesions is covered. The cuts are for the most part well reproduced. The book is an excellent summary of cardiac disease and should also be useful for quick reference.

Dentistry: An Agency of Health Service. By Malcolm Wallace Carr, D.D.S. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, $1.50. Pp. 219. New York: The Commonwealth Fund, 1946.

This book is interesting reading. It contains many facts concerning dentistry presented in a clearcut, brief and concise manner. It would serve an extremely useful purpose in public and high school libraries, in which young men and women interested in professional education might have access to it.

Principles of Hematology. By Russell L. Haden, M.D. Third edition. Price, $5. Pp. 366, with 171 illustrations. Philadelphia: Lea & Febiger, 1946.

The third edition of this book, like the others, presents to students and clinicians a readable and helpful presentation of the clinical aspects of diseases of the blood. It has been rewritten in part and now includes a section on the technic of bone marrow puncture and a description of the findings. It continues to be a most helpful clinical text.

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Manuscripts for publication, books for review and correspondence relating to the editorial management should be sent to the Chief Editor, Dr. N. C. Gilbert, 535 North Dearborn Street, Chicago 10. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago 10.

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